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EXPLORING THE CAUSAL NATURE OF NEIGHBORHOOD INFLUENCES ON VIOLENT CRIMINALITY, SUBSTANCE MISUSE AND PSYCHIATRIC MORBIDITY

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Exploring the causal nature of neighborhood influences on violent criminality, substance misuse and psychiatric morbidity
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Individuals who live in socioeconomically deprived neighborhoods, particularly in urban settings, experience elevated risk of being convicted of violent criminality, to engage in substance misuse and to be diagnosed with psychiatric disorders. The causal nature of these associations is questioned in the literature because previous studies have insufficiently accounted for genetic and environmental risks shared within families. The aim of the dissertation was therefore to explore the etiological relevance of neighborhoods in these traits by combining quasi-experimental, family-based research designs with nationwide Swedish registry data.

In Studies I and II, we investigated the associations between residence in deprived neighborhoods and family income during childhood on subsequent risks of being convicted of violent offences and to engage in substance misuse. We found that biological full-siblings who had been differentially exposed to deprived neighborhoods, due to residential relocations between their birthdays, or to family income, due to the parents' career trajectories, did not differ from one another in terms of their risks for being convicted or to engage in substance misuse.

In Study III, we studied the associations between neighborhood deprivation and population density on later risks of being diagnosed with schizophrenia. Biological full-siblings who had been differentially exposed to the different neighborhood conditions did not differ from one another in terms of their risks of schizophrenia.

In Study IV, we used quantitative genetic models that compared biological full and half-siblings to understand the etiology of social drift in schizophrenia. We found that the heritability of living in deprived neighborhoods was 60 percent. Schizophrenia patients were more likely to live in deprived neighborhoods but this was due to common genetic influences.

In conclusion, we found that familial risks simultaneously explained parental selection into high-risk neighborhoods as well as their offspring's increased risks of adverse outcomes. Methodologically, these studies emphasize the importance of accounting for unobserved familial confounders in epidemiological studies of socioeconomic status and later behavioral and psychiatric outcomes. Substantively, the findings indicate that efficient prevention efforts to decrease the rates of the examined outcomes must consider a broader range of familial and individual risks than merely socioeconomic and demographic measures, at least in the Swedish context.

LIST OF SCIENTIFIC PAPERS

I. Sariaslan A, Långström N, D'Onofrio B, Hallqvist J, Franck J, Lichtenstein P. The impact of neighbourhood deprivation on adolescent violent criminality and substance misuse: A longitudinal, quasi-experimental study of the total Swedish population. Int J Epidemiol. 2013;42(4):1057-66.

II. Sariaslan A, Larsson H, D'Onofrio BM, Långström N, Lichtenstein P. Childhood family income, adolescent violent criminality and substance misuse: quasi-experimental total population study. Br J Psychiatry. 2014;205:286-90.

III. Sariaslan A, Larsson H, D'Onofrio B, Långström N, Fazel S, Lichtenstein P. Does population density and neighborhood deprivation predict schizophrenia? A nationwide Swedish quasi-experimental study of 2.4 million individuals. Schizophr Bull. 2015;41(2):494-502.

IV. Sariaslan A, Fazel S, D'Onofrio BM, Långström N, Larsson H, Bergen SE, et al. Schizophrenia and Subsequent Neighborhood Deprivation: Revisiting the Drift Hypothesis using Population and Twin Genetic Data [Manuscript]

CONTENTS

LIST OF ABBREVIATIONS

A	Additive genetic influences
ASPD	Antisocial personality disorder
C	Shared environmental influences
CATSS	The Child and Adolescent Twin Study in Sweden
CD	Conduct disorder
CBCL	Child Behavior Checklist
CI	Confidence interval
CoS	Children of Siblings design
CoT	Children of Twins design
DSM	Diagnostic and Statistical Manual of Mental Disorders
DZ	Dizygotic (twins)
E	Unique environmental influences
GCTA	Genome-wide Complex Trait Analysis
GLM	Generalized linear model
GLMM	Generalized linear mixed-effects model
GWAS	Genome-wide association study
GxE	Gene-environment interaction
HR	Hazard ratio
ICC	Intra-class correlation
ICD	International Classification of Diseases
MBR	Medical Birth Register
MGR	Multi-Generation Register
MTO	Moving to Opportunities
MZ	Monozygotic (twins)
NCR	National Crime Register
NPR	National Patient Register
OR	Odds ratio

PSM	Propensity score matching
RCT	Randomized controlled trial
rGE	Gene-environment correlation
SAMS	Small Area Marketing Statistics
SES	Socioeconomic status
SUTVA	Stable Unit Treatment Value Assumption
TCHAD	The Child and Adolescence Twin Study
TPR	Total Population Register
WHO	World Health Organization

1 BACKGROUND

1.1 NEIGHBORHOODS AND PSYCHIATRY: A BRIEF HISTORY

1.1.1 Discovering geographical differences

The fact that psychiatric disorders and antisocial behaviors vary across geographical regions was one of the first discoveries in psychiatric epidemiology and related disciplines. Edward Jarvis[1], considered by many to be the founding father of the field[2], re-examined the 1840 US census data and observed stark differences in the distribution of psychotic disorders (termed insanity and idiocy at the time) across states and racial categories. Despite lacking adequate data on socioeconomic factors, Jarvis explicitly noted that the observed differences could, at least partially, result from such influences. His European contemporary, André-Michel Guerry[3,4] was the first scholar to combine cartographic methods with French census data to analyze the geographical distribution of numerous outcomes, including criminality and suicide. Guerry observed, for instance, that the rates of property crimes and suicides were elevated in the urban and socioeconomically affluent regions of the country.

Emilé Durkheim's[5,6] work on the social causes of suicide, which is still the prominent theoretical framework in the sociology of suicide[7], offers two mutually inclusive explanations as to why the rates of mental illnesses tend to cluster in urban settings. First, he argued, that the transition to densely populated modern cities weakened the social integration of individuals in the community to the extent that many lost their sense belonging to a social group. The *egoistic suicide*, as he termed it, denoted a suicidogenic process in which an individual fully detaches themselves from the influence of others and can only see their own actions as causing their various predicaments[5]. Suicide therefore becomes the only solution when the individual fails to validate their own existence[8,9].

Durkheim[5] was not only concerned with the changing nature of the social integration in the modern societies as they moved toward a higher degree of urbanicity, but also with of the moral deregulation that the transition implied; a phenomenon he termed *anomie*. Based on his observations that the rates of suicide increased during periods of both economic recession and growth, Durkheim argued that the inherent characteristics of the capitalistic market system (e.g. no

limits of earning potential and stark fluctuations in the financial institutions) contributed to individuals having unrealistic and ever-changing expectations, which in turns caused them frustration and confusion. The moral deregulation was therefore considered to be the key mechanism that explained increased levels of deviance, including suicidal behaviors.

1.1.2 The Chicago School and social disorganization

The city of Chicago; once a small agricultural town established in 1830 became a large metropolitan city by the turn of the twentieth century[10]. In the following three decades, the city roughly doubled its population size to over 3 million inhabitants[11]. The social implications of the new urban landscape gained the attention of a group of sociologists, led by Robert Park at the University of Chicago[12]. Their work formed the theoretical framework in which most, if not all, contemporary epidemiological neighborhood studies rests upon.

Park, who coined the term human ecology, argued that the structure and properties of social systems bore many resemblances to that of natural ecosystems[13]. The emergence of communities was therefore considered by him to result from the fact that individuals who shared similar backgrounds (*ecological niches*) were mutually dependent on one another (*symbiosis*). The separation of individuals into different social groups (*segregation*) was driven by *competition* through the market institutions for the acquisition of wealth and resources; the accumulation of which decided where the social groups lived. Ernest Burgess[14] expanded on these ideas by examining how the spatial distribution of social groups in the city changed as it expanded. By linking repeated measures of official statistics to maps of the city, he concluded that the city was divided into five concentric zones that expanded radially over time. The innermost zone included the central business district with all of the commercial enterprises. The remaining four zones consisted of residential areas that were socially patterned with increasing levels of socioeconomic deprivation the closer they were located to the innermost zone.

As the Chicago School researchers were primarily interested in studying social problems, they focused almost exclusively on the *zone in transition*, namely the slum area with tenements located right next to the polluting old factories in the business district. This was an area inhabited by newly arrived immigrants, day laborers from

rural parts of the country and senior citizens who simply had no other options. The booming economy led to a constant expansion of the business district and consequently the rates of residential mobility were high as the landlords were incentivized to sell their properties to business owners. Burgess[14] contended that social disorganization caused the accumulation of reproduction of social problems in the area. The concept of social disorganization was originally defined by Thomas and Znaniecki[15] as the diminishing influence of informal social control being exerted on individual members of a social group. Following in the tradition of Durkheim, social disorganization was thought to arise partly as a result of the residents being confronted multiple conflicting systems of norms and values (causing them confusion about social rules and the expectations of others), and partly because of the poor social integration resulting from the high levels of population turnover and the communication barriers.

The first empirical examinations of geographical differences in the incidence of criminality and mental illness within a city were published in the 1930s and 1940s. Shaw and McKay[16] tested whether the incidence of a wide range of indicators of antisocial behaviors (e.g. truancy, juvenile delinquency and adulthood criminality) differed across the concentric zones of Chicago; over the course of a four-decade period, the authors published a number of reports[17,18] replicating the observation that antisocial behaviors tended to cluster in the socially disorganized zone in transition. Faris and Dunham[19] used a similar approach in their study of the socio-spatial distribution of "insanity" (primarily schizophrenia) across the city of Chicago. The authors collected data on approximately 35,000 patients diagnosed with various mental disorders between 1922-1934 and estimated that the rate of "insanity" was elevated by a factor of 6.5 in the zone in transition as compared to the affluent zone located in the outskirts of the city. The authors did initially attribute their findings partly to the prevalent social isolation in the socially disorganized area but later work[20,21] either did not replicate the finding or suggested reverse causation[20,21].

1.1.3 Ecological fallacy and individualistic reductionism

A methodological debate erupted in the 1950s among quantitative social researchers regarding the statistical modeling of social processes that occur on different levels of abstraction[22]. For instance, the historic community studies of the

Chicago School[16,19] measured the exposure of interest on the level of the communities (e.g. social disorganization) while the outcomes were generally derived from individual-level data (police and hospital records). The complexity of the social disorganization theory[15], implying a cross-level interplay between structural community factors and individual behaviors, could however not be adequately modeled using the restricted models available at the time. The Chicago School scholars ultimately decided to focus on the community-level dynamics and adopted the ecological research design[23], which meant that they had to aggregate their outcomes to community-level measures (e.g. community incidence rates of delinquency and schizophrenia) and thereby ignore all individual-level variability.

William S. Robinson, a statistician who failed to recognize the theoretical complexity of these studies, thought that the "[e]cological correlations were used simply because correlations between the properties of individuals [were] not available" (p. 352)[24]. He went on to demonstrate individual and aggregate-level correlations between the same constructs were vastly different. By analyzing the 1830 US census data[24], Robinson observed a weakly positive association between individual measures of being foreign-born and illiterate ($r=0.12$), but a strong inverse association between state-level aggregates of the same constructs ($r=-0.53$). Although the term was coined later[25], the Robinson study is considered to be the first empirical examination of ecological fallacy, which denotes the invalid generalization of group-level findings to the individual level.

Critics of the Robinson study nevertheless argued that community dynamics could not simply be reduced to individual behaviors[26]. In fact, the notion that the sum of the society is greater than its individual parts has been a central tenet of sociological thinking since the nineteenth century[27]. The mechanisms operating on the micro and macro levels are certainly different but they could potentially influence one another. For instance, residing in a community with high rates of unemployment and criminality does not necessarily imply that unemployed individuals have a higher propensity to engage in criminality (ecological fallacy). However, the high rates of unemployment and criminality contribute to the social disorganization of the community, which in turn could potentially explain why other residents engage in crime (cross-level interplay).

1.2 ECO-EPIDEMIOLOGY AND CONTEMPORARY NEIGHBORHOOD STUDIES

The emergence of a wide range of chronic diseases throughout the postwar period transitioned epidemiology into the "black box era" of the discipline[28]. Single-cause models of diseases were gradually replaced by complex models, postulating that multiple and interacting risk factors contributed to the etiology of diseases[28]. Contemporary epidemiology have gradually entered into the eco-epidemiological stage, which is characterized by its emphasis on the integration of risk factors that operate on numerous levels of organization; from rare genetic variants in individuals up to community and even country-level social determinants[29-33]. The identified risk factors are generally viewed as being etiological agents, implying that they are causally related to the outcomes of interest[34]. The growing influence of the causal inference literature has nevertheless started to question the etiological relevance of many putative risk factors, including those that are measured in the community social context.

1.2.1 Development of multilevel models

One of the greatest advances in social statistics in the recent decades has been the development of statistical models that handle clustered data structures. A common assumption of many statistical models is that the individual observations must be independent, conditional on the covariates that the model accounts for[35]. In many cases, this assumption cannot be met. For instance, in the case of neighborhood studies, we know that neighbors tend to be more similar to one another than individuals who live in different neighborhoods, even after statistical adjustments for covariates. The same holds true for students in schools, siblings in families and patients in hospitals.

The development of generalized linear mixed-effects models (GLMMs) in the mid-1980s marked a new chapter in the field of social statistics, where applied researchers interested in neighborhood influences could simultaneously model for individual and neighborhood-level influences by decomposing the variance of an outcome of interest into two components; a neighborhood-specific variance component that measures *differences between neighborhoods* and the standard residual that measures *differences between individuals, within neighborhoods*[36]. Although the idea of variance decomposition dates back to Ronald Fisher's work on the analysis of

variance (ANOVA) models in the 1920s[37], the later developments offered flexible models that generalized to discrete outcomes, accounted for unbalanced datasets due to missing data, and were able to model for complex covariance structures[38,39]. The GLLMs were referred to as multilevel in the social sciences and in social epidemiology because of their ability to disentangle the effects of phenomenon occurring on multiple "levels" of abstraction[40-44]. The implementation of multilevel models in statistical software developed for applied researchers grew rapidly in popularity in the 1990s[45-47] and just within a few years, there was an exponential growth of the number of publications that had adopted such models[48-50].

1.2.2 Findings and causality

Recent systematic reviews that have examined multilevel neighborhood studies on antisocial behaviors and psychiatric disorders have found that the traits tend to be concentrated in socioeconomically disadvantaged neighborhoods, even after statistical adjustments for observed individual differences[48,51-55]. These effects tend to be stronger in countries with stark socioeconomic inequalities[56-59] and in the case of schizophrenia and related nonaffective psychotic disorders, there is additionally a clear urban-rural divide[60-64]. These combined findings suggest that there are factors, known as "contextual effects", operating on the neighborhood level that cannot be reduced to individual characteristics, or "composition effects"[43,65-67]. But are the contextual neighborhood effects causally related to these outcomes? The simple answer is that we do not know at this stage[48,52].

Researchers have since the 1960s attempted to disentangle two competing hypotheses about the causal nature of socioeconomic status and adverse psychiatric outcomes; social causation versus social selection[68-71]. Is it the case, as it is generally assumed in the literature, that individual risks for adverse behavioral and psychiatric outcomes increase as a function of exposure to adverse neighborhood influences (social causation) or does the observed individual risk increases result from unobserved risk factors that explain why they resided in such neighborhood environments in the first place (social selection)?

1.2.3 Confounding bias

One of the major issues in assessing the causal nature of associations between neighborhood influences and adverse outcomes relates to the fact that nearly all

neighborhood studies are based on observational, or non-experimental, research designs and may therefore be prone to substantial confounding[72,73]. Confounding refers to a systematic bias that arises in a situation where an exposure and outcome of interest are, either partially or completely, caused by a third variable, making the association between the exposure and the outcome spurious[74]. Researchers employ a wide range of strategies to address confounding bias in observational studies, ranging from statistical adjustments to stratification and matching procedures[74,75]. These strategies all assume, however, that the confounders are known and that they are subject to measurement. Such conditions are, unfortunately, rarely fulfilled.

A seldom discussed limitation of multilevel models is the implicit assumption that individuals choose their neighborhood in a completely random fashion[76], conditional on the modeled covariates. Estimates derived from multilevel neighborhood models are, contrary to popular belief[77], therefore highly likely to suffer from substantial confounding bias. It is by now well recognized that individuals tend to systematically choose their place of residence based on how well they match the characteristics of the targeted neighborhood population (e.g., in terms of the socioeconomic status[78-80], ethnic mix[81,82] and other demographic factors[83]). Such factors are in turn associated with criminality and psychiatric disorders. Recent findings from Sweden also indicate that there is an intergenerational transmission of residence in deprived neighborhoods, even after adjustments for socioeconomic status, family formation and ethnicity[84,85]. Given what we know about the familial aggregation of violent criminality[86,87] and psychiatric disorders[88,89], it is highly plausible that at least a proportion of such familial risks also predict neighborhood deprivation. The challenge is therefore to find an optimal way of quantifying familial risks in observational neighborhood studies.

Nationwide neighborhood registry studies that are commonly believed to provide reliable estimates of neighborhood influences on outcomes due to their large sample sizes only tend to include a few crude measures of family composition[61,62,90-94]. Importantly, there is a lack of detailed measures on the family dynamics that may confound the observed associations. Beyond such environmental factors, there are no adjustments for genetic risks. The latter is, however, difficult to incorporate using measured variables. In smaller samples, it is

possible to incorporate data on candidate genes. However, this approach is costly, requires a thorough understanding of the genetic architecture in order to guess how genetic loci (specific locations of genes in a chromosome) may be involved with socioeconomic status traits. Moreover, it has been shown that associations between candidate genes and psychiatric traits are notoriously difficult to replicate[95-97]. Other options include the polygenic risk scoring technique[98], which uses data from large-scale genome-wide association studies (GWAS) to calculate genetic risk indices for specific outcomes in individuals who have been genotyped. GWA studies in psychiatric genetics are costly, still largely underpowered and given the focus on common genetic variants, they expectedly explain a relatively small proportion of variance in studied traits[99,100].

1.2.4 Experimental designs

The absence of accurate ways of accounting for unmeasured familial confounds in observational studies have therefore encouraged researchers to consider alternative research designs. Experimental designs, such as the randomized controlled trial (RCT), offer a simple yet a powerful solution to account for both observed and unobserved confounders. The rationale of the design is to allow for the random assignment of study participants to different exposure groups (e.g. an intervention and a control group) and thereby average out any differences in confounding factors between them[74]. If a difference is observed in the outcome between the groups at the end of the follow-period, it is generally thought to result from the intervention. The importance of accounting for unmeasured confounders using RCTs has been demonstrated in the literature examining the effects of vitamin supplementation on health outcomes[101]. For instance, while large-scale observational studies with multiple adjustments for observed confounders found strong protective effects of vitamin E supplementation on the risk of developing cardiovascular diseases[102,103], seven RCTs failed to observe any meaningful differences[104].

Randomizing vitamin supplements to participants is one thing, but would it be feasible to use a randomized research design to study neighborhood influences? The list of limitations would certainly advise against it as it includes the inability to assign participants to adverse exposure conditions due to ethical considerations, requirement of large samples to reliably average out confounding differences

between the exposure groups, minimization of potential selection bias and sample attrition to increase the external validity and the fact that complex interventions introduce a multitude of components outside of the control of the researcher[74,105-107].

The Moving to Opportunities (MTO) project, a research program sponsored by the US Department of Housing and Urban Development, attempted to defy the odds when it recruited around 4,600 socioeconomically disadvantaged female-headed families, predominantly of African-American and Hispanic heritage, in the mid to late 1990s and followed them up for about a decade and a half[108]. The participating families were randomized into two experiment groups and one control group. The first experiment group was offered rental assistance vouchers that could only be used in census tracts with a poverty rate below 10 percent. The second experiment group was offered similar vouchers but did not have the same restrictions in terms of the location of their new residence. The control group did not receive any vouchers but were eligible to apply for the benefits that they would have been otherwise entitled to.

The final evaluation report of the project found that neighborhood influences did not impact criminality, substance misuse, educational attainment and labor market participation outcomes after the full 12-14 year follow-up period[108,109]. The neighborhood effects on mental health outcomes were inconsistent; the sex-stratified analyses showed that the female participants reported reduced levels of mental health problems while the reverse was true for the male participants. The interim reports that were produced after 5-7 years of follow-up found similar inconsistencies; while the male participants reported higher rates of property crimes and other behavioral problems compared to controls, the female reports indicated reduced rates of the same outcomes compared to controls[110,111]. Some have speculated that these inconsistent findings may have been due to differential exposure to sexual predation among the females as they moved to areas with less concentrated disadvantage[112].

It is far from clear how the results of MTO should be interpreted. Despite its intention to address the issue of unmeasured confounding in the neighborhood literature, it could be argued that the project has in fact added bias of unknown magnitude and direction by its design. Selection bias is obviously an issue, given

the focus on impoverished female minorities with children. The list of limitations is extensive but some of the key issues that undermine the possibilities of drawing causal inferences based on the presented data include that (a) the participants had to actively apply to be recruited to the project (and the fear of safety was commonly the reason for their participation[113,114]), (b) a large proportion of those who did receive their vouchers decided not to use them and (c) those who did were free to relocate at any time during the follow-up period, and (d) none of the participants were assigned to relocate to a more deprived community as this would be unethical[108].

Although impressive in its scope and ambition, the contribution of the MTO project to the causal inference of neighborhood influences on adverse outcomes remain minimal at best. Sociologists have deemed the project to engage in individual reductionism for its alleged lack of focus on social contextual and temporal mechanisms (e.g. influences of accumulated disadvantage)[82,115]. Michael Oakes, a social epidemiologist who assert that "an experimental methodology is possible and superior"[116] (p. 1929) to examine neighborhood influences, still questions the extent current parameter estimates derived from observational studies are confounded[117,118]. There is therefore a need to adopt alternative research strategies to understand the causal pathways in which neighborhood influences might impact its residents.

2 THE OUTCOMES

2.1 VIOLENT CRIMINALITY AND SUBSTANCE MISUSE

2.1.1 Violence as a global public health concern

There has been an increasing interest within epidemiology to understand the etiology of violence over the last two decades following the declaration of the World Health Assembly that the prevention of violence is a global public health priority[119,120]. Although encumbered with numerous methodological limitations, the World Health Organization (WHO) estimated that 1.6 million individuals died in 2000 due to violence of any form, a third of which were attributed to interpersonal violence[121,122]. The WHO published an action plan implementation report four years later where they specifically targeted both substance misuse and within-country income disparities as important risk factors of violence[122].

The financial burden of violence is tremendous; estimates from the United States indicate that the costs account for an excess of three percent of the country's gross national product[123], with over 92 percent of the costs being attributed to lost productivity[124]. Similar estimates have been reported from other countries[121,123]. Importantly, the burden of violence cannot even be expressed when it comes to the suffering of the victims and their families.

2.1.2 Diagnostic classification

Violent criminality and substance misuse are generally classified as "externalizing problems" in the psychopathological literature[125]. The distinction between externalizing and internalizing problems dates back to the late 1970s, when Thomas Achenbach and Craig Edelbrock applied psychometric approaches to survey data on a wide range of emotional and behavioral symptoms in school children[126-128]. Their findings indicated that the measured symptoms tended to be explained by two second-order factors or "broad-band groupings" that they termed externalizing and internalizing problems. The authors characterized externalizing problems as an undercontrol of emotions that increased the child's propensities to engage in rule-breaking behaviors and generated difficulties for them to have non-aggressive and meaningful interactions with others. Internalizing problems were, conversely, characterized as an overcontrol of emotions that increased the child's feelings of worthlessness, demands for attention while

withdrawing socially. The literature has since this period repeatedly replicated the existence of these two clusters of symptoms and genetically informative studies have established etiological differences between them[129-139].

Violent behaviors are described in the fifth and latest revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as stemming from two types of related disorders; conduct disorder (CD), which includes early-onset aggressive and rule-breaking behaviors, and antisocial personality disorder (ASPD), which is the diagnosis given to individuals over 18 years of age who experience persisting symptoms of conduct disorder and who have additionally developed deceitfulness and a lack of remorse[140]. The prevalence of CD has been found to range between 1.8 to 16 percent[141] while equivalent estimates for ASPD range between 0.2 to 3.3 percent[140].

The clinical classification of substance misuse (e.g., alcohol and illicit drugs) has been and continues to be the subject of an intense debate. The latest revision of the DSM included a number of substantial changes to the classification. The previous diagnostic categories of substance abuse and dependence, where the latter implied a higher degree of severity, were collapsed into one diagnostic category named substance use disorders[140]. Individuals who fulfill at least two of a total of 11 diagnostic criteria that cover problematic use, whether the use has come to the attention of clinical professionals and/or compromised the individual's social functioning are diagnosed with having a substance use disorder. The lifetime prevalence of alcohol use and dependence has been estimated to 6.4 percent[142] in the United States while the equivalent estimate for drug abuse and dependence is 8.9 percent[143]. A review paper examining the 12-month prevalence of alcohol dependence in Europe found that the estimate for males was 6.1 percent, while the equivalent estimate for females was 1.1 percent[144].

2.1.3 Etiology

Systematic reviews have generally found that antisocial behaviors (e.g., CD and ASPD) and broader measures of externalizing problems (e.g., antisocial behaviors, substance misuse and disinhibited personality) have a heritability of approximately 50 percent[145,146], with aggressive behaviors being more heritable than nonaggressive rule-breaking behaviors[147,148]. Behavioral genetic studies that have focused on the etiology of specific substance use disorders have also shown that the traits are

considerably heritable but that important environmental contributions are present as well[149-153]. A longitudinal Swedish twin study found that shared environmental influences were particularly important for the development of antisocial behaviors when the study participants were in their early adolescence, between ages 13 and 14 years, likely due to the potential peer influences[154]. Recent nationwide registry studies examining peer influences on drug misuse, as indexed by future drug misuse behaviors similarly aged neighbors, has also emphasized the importance of peer influences[155]. A variety of socioeconomic status indicators have been linked to both violence and substance misuse in large-scale studies[156-158] and in small quasi-experimental studies with potential selection bias[75,159,160]. It remains unclear to what extent socioeconomic factors are relevant for the etiology of violent criminality and substance misuse.

2.2 SCHIZOPHRENIA

Schizophrenia is among the most severe and chronic psychiatric disorders with an estimated lifetime prevalence ranging between 0.7 and 0.8 percent[161,162]. The discovery of concept of the disease often attributed to Emil Kraepelin who in the late nineteenth century introduced it as a form of dementia (dementia praecox), characterized by an early onset during late adolescence with a rapidly deteriorating clinical course[163]. The clinical presentation of patients with schizophrenia is heterogeneous as the patients suffer from a range of positive and negative psychotic symptoms in combination with cognitive impairments. The positive symptoms include delusions (e.g., false beliefs despite strong evidence to the contrary) and hallucinations (e.g., the experience of an event, either auditory or visually, without any external physical stimuli) while the negative symptoms involve compromised motivation, mobility, speech and ability to engage emotionally in social interactions.

2.2.1 Etiology

Etiological studies of schizophrenia demonstrate that the familial contributions are substantial. Familial aggregation studies indicate that first-degree relatives of a proband with schizophrenia experience a ten-fold increased risk of being diagnosed themselves[164]. Unaffected siblings have additionally been found to experience higher rates of psychotic symptoms, cognitive impairments and language problems compared to population controls[165,166]. A meta-analysis of twin

studies indicates that the heritability of schizophrenia is approximately 80 percent[167], a finding that has been largely replicated in nationwide Swedish quantitative genetic sibling studies[88,89]. It is estimated that approximately a quarter of these heritability estimates can be attributed to common genetic variants[168]. The search for common genetic variants that are associated with schizophrenia in GWA studies has been fruitful as recent findings have identified 108 loci (e.g., locations in the human genome) that are associated with the disorder, which provides biological clues into the underlying etiology[169].

A number of putative environmental risk factors have additionally been identified in the literature, including birth and residence in urban environments[51,60-62,170,171], socioeconomic deprivation[52,53,77,172,173], frequent relocations[174], migration[175-177], and paternal age at birth[178-180]. Systematic reviews emphasize the importance of neighborhood influences[52] but there are no studies to date that have examined the relative importance of unobserved familial confounders in the associations between these environmental risks and schizophrenia[181].

3 MATERIALS

Studies I-III were all based on data derived from the Swedish nationwide registries while Study IV additionally included data from the Child and Adolescence Twin Study (TCHAD).

3.1 SWEDISH NATIONWIDE REGISTRIES

Sweden's long history of gathering nationwide registry data dates back to the mid-18th century[182]. All permanent Swedish residents have ever since 1947 been provided with a unique personal identification number (PIN; *personnummer*), either upon birth or in connection to their immigration to the country[183]. Similar systems are established in the entire Nordic region[184]. The number itself consists of ten digits, the first six of which identifies the individual's date of birth and the remaining ones are combinations of random and control numbers[183]. The PIN is systematically utilized in by governmental agencies in their routine collection of data that links individuals with the specific services that the agencies provide (e.g., health care, prison services, education etc.).

Statistics Sweden is the governmental agency that is responsible to maintain and to develop registries that include such data. The PIN therefore enables them to generate very large datasets that include services provided by multiple agencies over time. Researchers affiliated with recognized Swedish universities and colleges are able to use de-identified data in their research following an approval from independent ethical review boards.

3.1.1 Description of the registries

The following nationwide Swedish registries were utilized in the present thesis:

- **Total Population Register (TPR)**: Established in 1967 following the complete computerization of the Swedish Tax Agency's administration and currently maintained by Statistics Sweden[182]. The TPR includes basic demographic information (e.g., sex, birth date, country of origin, registered residential address as well as the dates of migration and mortality) on all Swedish residents who were born after 1932 and who were alive in 1968.

- **Multi-Generation Register (MGR)**: The MGR links all index persons available in the TPR to their biological (and if applicable, adoptive) parents. The data coverage in terms of maternal links is complete for all individuals born in Sweden since 1950 while the individuals who were born in Sweden since 1950 are all linked to their biological mothers and 98 percent are linked to their biological fathers[185]. The coverage for immigrants vary according their date and age at immigration[185]. We used the MGR to identtify all biological full-siblings (individuals who share both of their parents; Studies I-IV), maternal and paternal half-siblings (individuals who either share their mothers or fathers; Study IV) as well as full-cousins (individuals who share their grandparents; Studies I-III).

- **Medical Birth Register (MBR)**: The MBR is held by the National Board of Health and Welfare (*Socialstyrelsen*) and includes nearly all (approximately 1-2 percent missing) births given in Sweden since 1973[186]. The register includes a information on a wide range of perinatal factors as well as behavioral measures of the mothers. The MBR was used as the base sample in Studies I and II.

- **Small Area Marketing Statistics (SAMS) Register**: SAMS is a geographical classification system including around 9,200 residential areas in Sweden. The aim of the SAMS classification is to provide a theoretically meaningful definition of residential areas (cf. census tracts or parishes) by delineating socioeconomically homogenous areas based on the local housing distribution[187]. Statistics Sweden has since 1982 annually assigned Swedish residents to SAMS areas based on their registered address at the end of each year. The definitions of SAMS areas differ across the country based on the population density; whereas the national average population size per area is approximately 1,000 inhabitants, the equivalent estimate for Stockholm is slightly above 4,000 inhabitants[188]. Some critics have argued that the socioeconomic homogeneity aim is not entirely reached and propose instead the development of new classification systems based on detailed geographical information systems[189] or individual-centered approaches (e.g., k-Nearest neighbor aggregates)[190,191]. However, when individuals are asked about their neighborhoods, they are generally able to delineate virtually

identical SAMS areas[192]. The SAMS classification is therefore currently the best available measure on neighborhoods in Sweden on a total population level[193]. Data from the SAMS register was used in Studies I and III-IV.

- **National Patient Register (NPR)**: The NPR is held by the National Board of Health and Welfare and includes diagnosis codes as well as admission and discharge dates for inpatient care hospitalizations in public hospitals since 1973. Out-patient visits to specialist physicians in public and private practices are included since 2001 although the coverage is limited before 2006. The registry does not include data on patients who have received medical services in the primary care or other care services provided by non-physicians (e.g., psychologists and physiotherapists). The diagnosis codes in the NPR are classified according to the International Classification of Diseases; ICD-8 (1969-1986), ICD-9 (1987-1996) and ICD-10 (1997-2009).

- **National Crime Register (NCR)**: The NCR is held by the National Council for Crime Prevention (*Brottsförebyggande rådet*) and includes complete records of all criminal convictions in Swedish lower courts since 1973. This includes non-custodial sentences and cases where the prosecutor either cautions or fines the defendant. It is important to note that plea bargaining practices are prohibited within the Swedish legeal system and that the legal age of responsibility in Sweden is set to 15 years, which implies that the NCR has no data on criminal convictions for individuals younger than this age limit. The NCR was used to define violent criminality and substance misuse (Studies I-II) as well as neighborhod crime rates (Studies I, III-IV).

- **The Primary School Register (PSR)**: The PSR is held by the Swedish National Agency for Education (*Skolverket*) and includes data from records of school performance at the end of the nine-year primary school (*grundskola*), when the students are between 15 and 16 years of age. The register has been updated annually since 1988 and was revised in 1997 following a fundamental change of the school mark system. Each student is linked to their performance in all school subjects and the schools they last attended. The latter point is important to note as the register lacks data on

school mobility; only the final grades given in the last year are included. We used data from the PSR in Study I to link children who attended the same schools and to calculate their grade point averages.

- **Education Register:** The Education Register (1985-) is an annually updated nationwide register held by Statistics Sweden that primarily measures the highest achieved level of education in the population. We used the register to generate an neighborhood indicator measure of low educational attainment (Studies III-IV)

- **Longitudinal integration database for health insurance and labor market studies (LISA) Register**: The LISA register (1990-) is a comprehensive annual census database held by Statistics Sweden for all Swedish residents over the age of 15 years that includes a wide range of socioeconomic (e.g., income, educational attainement, unemployment and social benefits) and sociodemographic (e.g., marital status, family constellation and number of residential relocations) measures. The LISA register was used to define childhood family income and welfare recipiency (Study II) as well as to generate indicator variables for the neighborhood deprivation measure (Studies I, III-IV).

- **The Swedish Population and Housing Censuses (HC):** Prior to the development of the LISA registers, the nationwide censuses were conducted by Statistics Sweden every fifth year between 1960 and 1990. The response rates were nearly perfect throughout the whole period (only 2.5% missing cases in the 1990 HC)[194]. In Studies III-IV, we used the 1985 HC to calculate an indicator measure of the neighborhood prevalence of divorced individuals.

3.1.2 Generated measures

3.1.2.1 Neighborhood deprivation (Studies I, III-IV)

The level of neighborhood deprivation was defined by a number of key aggregated characteristics of the population residing in the neighborhoods. The comprehensive neighborhood deprivation score could only be calculated for 1990

and onwards because of its dependence on data from the LISA registers. For each neighborhood and year, we generated the following indicators for all residents who were between 25 and 64 years of age:

- Median neighborhood income
- Proportion with low educational attainment
- Proportion unemployed
- Proportion divorced
- Proportion immigrants
- Residential mobility
- Neighborhood crime rate

These indicators were subsequently analyzed using a principal components analysis model, where a single-component solution emerged as the best fitting model across the examined period. This component was used as the standardized neighborhood deprivation score. In Studies III and IV, we wanted to derive similar scores for the years between 1982 and 1989 to increase statistical power. We decided therefore to test whether using four indicators (proportion with low education attainment, divorced and immigrants as well as the crime rate) would correspond to the comprehensive measure. The correlation between the scores of the comprehensive and limited deprivation measures for the years between 1990 and 2009 was very high (r=0.93), suggesting that the measures essentially captured the same neighborhoods.

3.1.2.2 Violent criminality (Studies I-II)

Violent crime was defined as a conviction for homicide, assault, robbery, threats and violence against an officer, gross violation of a person's/woman's integrity, unlawful threats, unlawful coercion, kidnapping, illegal confinement, arson, intimidation, or sexual offences (rape, indecent assault, indecent exposure or child molestation, but excluding prostitution, hiring of prostitutes or possession of child pornography)

3.1.2.3 Substance misuse (Studies I-II)

Substance misuse was defined as convictions of any drug-related crimes (defined as crimes against the Narcotic Drugs Act (SFS 1968:64) or driving under the influence of alcohol and/or illicit substances) or having been diagnosed with an

alcohol or drug-related disease in the NPR (ICD-8: 291, 303–4, 571, E853, E856.4, E859, E860, N980; ICD-9: 291, 303–5, 357.5, 425.5, 535.3, 571.0–571.3, E850, E854.1–2, E855.2, E860, N980; ICD-10: F10, G32.2, G62.1, G72.1, I42.6, K29.2, K70, K85, X41–2, X45, X61–2, X65, Y11 (with T43.6), Y12 (with T40) and Y15 (with T51)).

3.1.2.4 Childhood family income (Study II)

Childhood family income is a proxy measure of the material living standard of children in Sweden. We derived data on family disposable income (net sum of all earnings and benefits provided by the state) for both biological parents of each offspring. The income measures were subsequently inflation-adjusted to 1990 values using data on the development of the consumer price index, as provided by Statistics Sweden. In cases where the biological parents were separated, the offspring were assigned the mean value of both biological parents' family incomes.

3.1.2.5 Population density (Study III)

We generated two separate definitions of population density based on the available data:

- *County definition*: The TPR register enabled us to link all individuals who were born in Sweden to their county of birth (21 counties in total). We generated annual population density scores for each county by dividing the population size with the areal size of the county.

- *SAMS definition*: From 1982 and onwards, we were able to increase the variability of the density score by using the SAMS classification system that includes an excess of 9,200 residential areas. We generated the population density scores in a similar fashion by taking the annual population size divided by the areal size of the SAMS areas.

3.1.2.6 Schizophrenia (Studies III-IV)

To minimize false-positive cases in the main analyses, we defined study participants diagnosed with schizophrenia (ICD-8/9: 295; ICD-10: F20-21) on at least 2 separate occasions as having the disorder. Broader definitions were used in sensitivity analyses.

3.2 TWIN STUDY OF CHILD AND ADOLESCENT DEVELOPMENT

The Swedish Twin Registry (STR) was established in the 1950s and is currently the largest register of twins worldwide with an excess of 194,000 twins[195]. Beyond the impressive sample sizes that the research group has acquired over the last decades, one of the key strengths of the project involves linking extensive survey data with the nationwide population registries.

The Twin Study of Child and Adolescent Development (TCHAD)[196] is one of many population-based longitudinal twin studies included in the STR and focuses on all twins that were born in Sweden between May 1985 and December 1986 (n=2,960). The twins and their parents were sent mail questionairres during four separate occassions (Wave I: 1994; Wave II: 1999; Wave III: 2002; Wave IV: 2005). The parental response rates varied between 73 and 78 percent while the twin response rates varied between 52 and 82 percent.

We used parental data from the three first waves of the TCHAD study in Study IV.

3.2.1 Psychotic experiences

We defined children who had psychotic experiences based on parental reports of offspring auditory hallucinations, anytime between the three first waves, according to the following item in the Child Behavior Checklist (CBCL[197]): "Does your child hear sounds or voices that aren't there?" At least one endorsement across the waves sufficed for the classification. Parental reports of auditory hallucinations are strong predictors of general psychotic experiences[198,199].

4 METHODS AND CAUSAL INFERENCE

4.1 THE COHORT RESEARCH DESIGN

All of the studies presented in this dissertation are based on prospectively gathered observational data derived from the nationwide Swedish registries (see section X.1 for details). The studies have adopted the cohort research design, where a population at risk are selected and classified according to their level of exposure to a given risk marker, and subsequently followed up with respect to whether or not they experience a given outcome[74]. The word cohort is defined as a group of individuals who are followed up over time, and in most instances the group refers to a set of individuals who share the same birth years and are referred to as birth cohorts[200,201]. At the end of the follow-up period, it is possible to estimate the absolute and relative risk differences between the exposure groups[202].

The general approach we undertook when designing the studies can be summarized in the following three steps:

1) A base sample of birth cohorts from the TPR or MBR was selected depending on the availability of exposure and outcome data. Younger cohorts (born 1973 and later) included in the MBR had additional information on birth characteristics.
2) Study participants were classified according to their exposure status and we included additional confounding variables as well as the outcome(s) of interest.
3) Study participants were followed up until they either experienced the outcome of interest, migrated or died, whichever occured first.

4.2 THE COUNTERFACTUAL FRAMEWORK

The counterfactual perspective is an influential theoretical and philosophical framework in the field of causal inference, the genesis of which is often attributed to the contributions of Neyman and Fisher in the 1920s as well as Rubin since the mid-1970s[203-209]. The term counterfactual refers to a condition that is contrary to facts. For instance, if we were to observe a person (denoted as u) who had grown up under socioeconomically deprived circumstances (the treatment, t) being convicted of a violent crime (the outcome, Y), we could engage in a counterfactual thought experiment and ask whether the same outcome would have occurred if

the same person had grown up under affluent circumstances (counterfactual control, c) instead. To establish causality between the treatment (exposure to neighborhood deprivation) and outcome (violent conviction) in this particular individual, we would need to estimate the following:

$$Y_t(u) - Y_c(u), \qquad \text{[Eq. 1]}$$

or the difference between the outcome when the individual is exposed to the treatment (Y_t) compared to the outcome when the individual is exposed to the counterfactual condition (Y_c). Following the same logic, the average causal treatment effect (T) in the population is defined as the difference between the expected values of Y_t and Y_c:

$$T = E(Y_t) - E(Y_c) \qquad \text{[Eq. 2]}$$

The "fundamental problem of causal inference"[210] (p. 947), is nevertheless that we can only observe the factual conditions, not the counterfactual ones. The point of the counterfactual perspective is to demonstrate that the estimation of causal treatment effects requires exchangeability, namely that the study participants must have an equal chance of being allocated to any of the exposure groups[211]. Confounding and selection biases therefore hinder researchers from drawing causal inferences by generating non-exchangeability of the participants between the different exposure groups.

Nearly all studies, regardless of whether they are experimental, quasi-experimental or non-experimental, violate the exchangeability assumption to some degree. This is only one of many reasons for why a single study cannot determine causality. Randomized studies may theoretically come close to fulfilling the assumption, given sufficient statistical power, the lack of selection bias and adequate treatment adherence. Such circumstances are nevertheless hard to achieve in practice.

4.2.1 Propensity score matching

The propensity score matching (PSM) technique, developed in the 1980s by Rubin and Rosenbaum, is an increasingly popular counterfactual approach that aims to improve exchangeability between exposure groups in non-experimental research designs[212]. A simplified rationale for the approach can be explained in the following four steps[38,213,214];

(1) Observed data gathered prior to the time of exposure are used to estimate a propensity score (e.g., a predicted probability) for each participant to end up in different exposure groups.
(2) The covariates used in the previous step are balanced so that their distributions within each stratum of the score are similar.
(3) Individuals with similar propensities but with different exposures are matched.
(4) Different multivariate models are used to estimate the association between the exposure and outcome depending on the type of matching approach that is adopted in the previous step.

The major drawback of the PSM approach, as well as its modern longitudinal extensions[215], is their reliance on observed data to measure propensities. The presence of unobserved genetic and environmental confounders will contribute to systematic differences between individuals with similar observed propensities, which compromises the exchangeability assumption. PSM has furthermore been found to be highly sensitive to specification errors[216-218] and some critics have argued that the findings rarely differ from standard regression techniques[219,220].

4.3 FAMILY-BASED RESEARCH DESIGNS

The neighborhood literature is currently standing at a crossroads where non-experimental research designs have shown to estimate biased model parameters due to their inability to account for unmeasured confounders while experimental research designs have shown to be difficult, if not impossible, to be carried out. This situation is, however, not unique to the neighborhood literature but is, with only a few exceptions, a general problem in epidemiology and in the social sciences[105].

Behavioral genetics has approached this issue in a slightly different way. The field has developed a variety of quasi-experimental research designs that take advantage of genetically informative datasets to test different causal hypotheses[221]. Quasi-experiments or natural experiments imply that the researcher takes advantage of naturally occurring phenomenon, which in this context refers to the use of data on family relationships[222]. The classical twin and the adoption designs have been used extensively in the last three decades but the methodological development within the field has also brought the application of new research designs, including

complex multivariate twin models, quantitative genetic models using multiple sibling comparisons and intergenerational children-of-twins/siblings designs (CoT/CoS)[221,223,224].

4.3.1 The classical twin model and heritability estimates

The purpose of the classical twin model is to estimate the relative contributions of genetic and environmental influences in a given phenotype (an outcome of interest). The model rests on the following three assumptions; (1) identical (monozygotic, MZ) twins share all of their co-segregating genes, (2) fraternal (dizygotic, DZ) twins share half of their co-segregating genes and (3) all twins share their childhood family environments. By combining phenotypic data on twins with this model, the researcher is able to decompose the phenotypic variation into three distinct components; (additive) genetic, shared environmental influences and unique environmental influences[225].

The additive genetic component is referred to as the heritability of the phenotype. Shared environmental influences include all environmental factors that are shared by the twins within the family while unique environmental influences include factors that are unique to each twin. Given the assumptions, we expect monozygotic twins to be more similar to one another in terms of the phenotype compared to the dizygotic twins if genetic influences are etiologically important for the phenotype. The classical twin design may be extended to full and half-siblings to increase statistical power and generalizability of the findings[88,223,226]. It should be noted, however, that the generalizability for twin studies remain high, especially in regards to antisocial behavior outcomes[227].

Heritability estimates are often the subject of an ecological fallacy; the term does not denote the percentage of genes in an individual that causes the given phenotype but the genetic contributions to the phenotypic variance in the studied population[228]. The relative contributions of genetic and environmental influences in two separate individuals who develop the same disorder could be vastly different from one another. What the twin study does is to estimate an average of such influences in a given population and time period. This distinction is important to recognize as it implies that the heritability estimate is dependent on the studied population as well as the time of measurement. It should be noted, however, that meta-analyses of heritability estimates for common phenotypes in

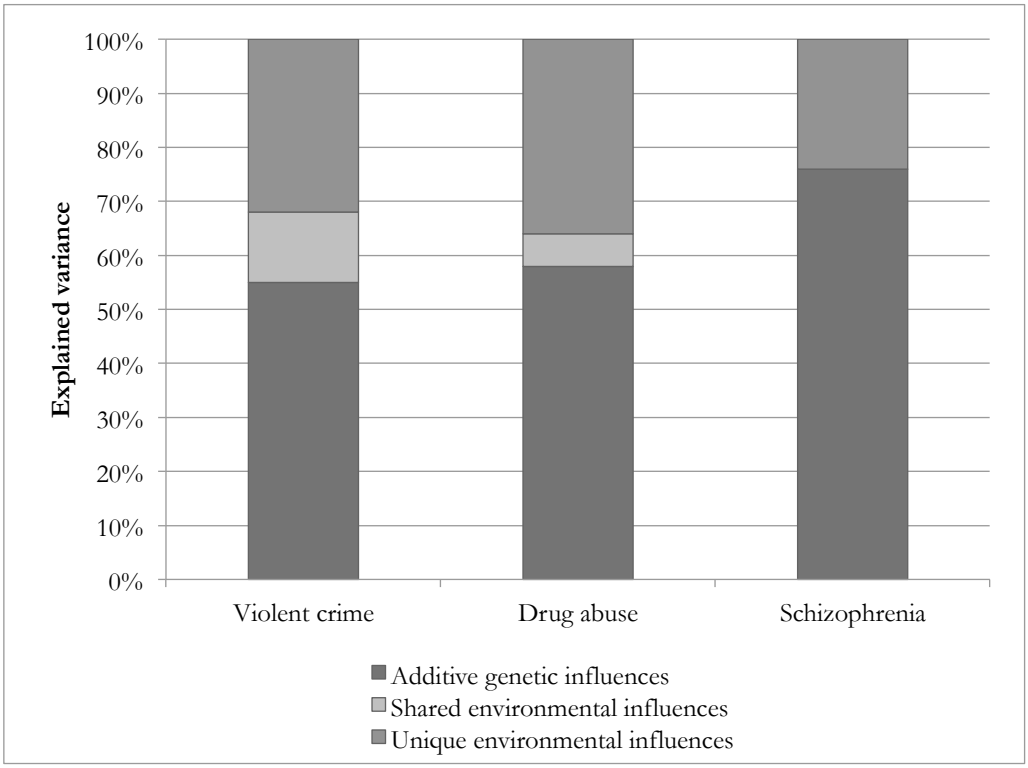
psychiatry tend to indicate, given large enough sample sizes and similar measures, relatively stable estimates across studies.

4.3.2 Etiology of the phenotypes

Eric Turkheimer, the former President of the Behavior Genetics Association, summarized the contributions of the field in the following three laws; (1) all behavioral traits are under some form of genetic control, (2) shared environmental influences are smaller than genetic influences and (3) a sizeable proportion of the variation in behavioral traits are not due to either genes or shared environments[229] (p. 160). These observations are consistent with what quantitative genetic studies using nationwide Swedish registry data has found for violent criminality[87], illicit drug abuse[89] and schizophrenia[89] as illustrated in Figure 4.1.

In accordance with the first and second laws, Figure 4.1 demonstrates that an excess of half of the variance in all phenotypes are attributed to genetic influences. Shared environmental influences are negligible in schizophrenia and remain small for both violent crime and illicit drug abuse. In line with the third law, it can be observed that a quarter to a third of the phenotypic variances is due to unique environmental influences, which also includes measurement error. Two factors are important to note here; Swedish etiological findings for violent criminality deviate from a recent global meta-analysis, which included 103 twin and adoption studies and found negligible effects of shared environmental influences on aggressive antisocial behaviors[145,147,148]. Moreover, in similar studies of illicit drug abuse in Sweden, there have been indications that the shared environmental influences are primarily important for males but negligible for females[230] .

Figure 4.1 Genetic and environmental influences on violent crime, drug abuse and schizophrenia



4.3.3 Gene-environment correlations

The decomposition of the phenotypic variance into components that measure shared and unique environmental influences is not particularly informative in terms of identifying specific environmental factors that are etiologically relevant for the development of a given behavioral and/or psychiatric phenotype. Behavioral geneticists have therefore moved beyond fitting the classical twin model and focus instead on understanding the causal mechanisms that link specific environmental risk factors to phenotypes by adopting various family-based research designs[221,231-234].

Social epidemiological studies often fail to recognize that many of the traits that are considered to be environmental are also, to varying degrees, heritable; a phenomenon known as the "nature of nurture" or "gene-environment correlation (rGE)" in the literature[235,236]. According to this perspective, environments act "as extended phenotypes, reflecting genetic differences between individuals as they select, modify, and construct their own experience of the world" (p. 90)[237]. Three

distinct ideal types of rGE have been identified in the literature; passive, active and reactive rGE[238,239].

- **Passive rGE**: Offspring receive their genes and their childhood environments from their parents and these factors are therefore likely correlated. For instance, an offspring whose parents have antisocial behavioral problems (e.g., extensive criminal records, and a history of substance misuse) will face increased risks of developing such behaviors themselves, partly due to their inherited genes and, to a lesser extent, the deleterious environments that they are exposed to during their childhood and adolescence (e.g., poor child rearing practices, low material living standard, parental conflicts and separation etc.). Passive rGE suggests that the parental genes also contribute to the generation of such environments; numerous indicators for childhood environments have been found to be at least moderately heritable[240-242]. A recent US study have further identified associations between risk indices of dopaminergic genes that have been tentatively linked to antisocial behaviors (e.g., DAT1,DRD2 and DRD4)[243,244] with residence in deprived neighborhoods[245]. The latter findings must be interpreted cautiously as a recent systematic review failed to find any meaningful candidate gene predictors of violence and aggression[246]. Together, these findings underline the importance of considering passive rGE mechanisms.

- **Active rGE**: The environments that an individual selects and modifies as they age are correlated with their genetic propensities. The offspring with antisocial parents in the example above will, for instance, based on this concept, have a higher propensity due to its genetic propensities to seek and influence peers in the school environment who explicitly demonstrate antisocial tendencies and behaviors. This mechanism has been supported in empirical investigations of different types of antisocial peer affiliation, where the findings have generally indicated that such traits are moderately heritable[242,247-252]. Active rGE emphasizes the relative importance of genetic factors in non-random self-selection into specific types of environments, which includes residence in deprived and urban

neighborhoods in adulthood.

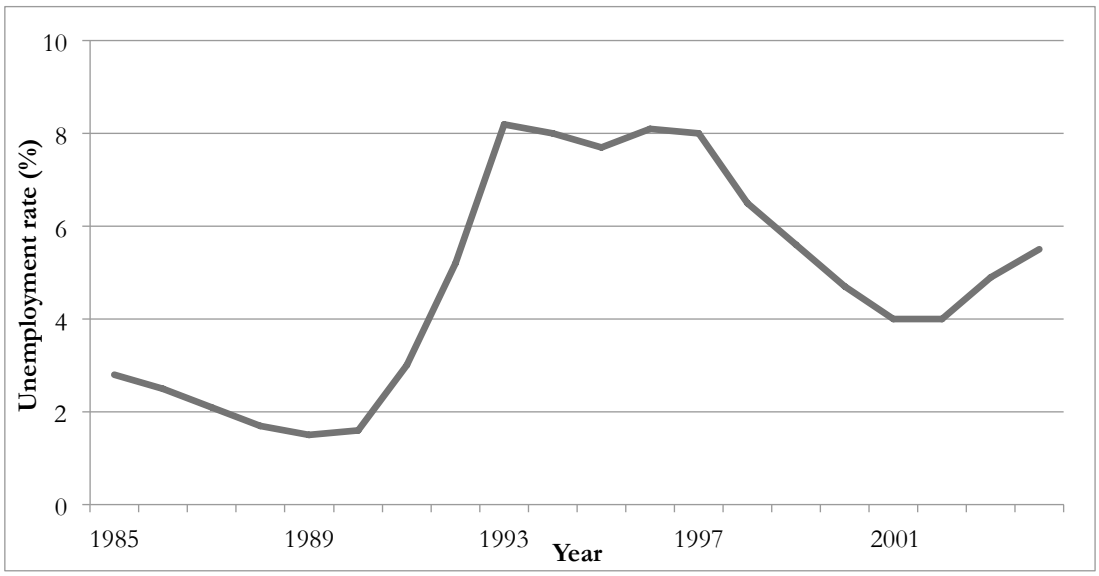
- **Reactive or evocative rGE**: An individual's genetic propensities to develop certain personality and behavioral traits may "evoke" differential environmental reactions. For instance, children with impulsivity and inattention problems will tend to be treated differently by teachers in the classroom setting (e.g., being more supervised) when compared to children who lack such problems. Recent studies have found evidence for evocative mechanisms to play a role in maternal control traits in general[253] and specifically in regards to offspring internalizing problems on maternal emotional overinvolvement[254] and offspring externalizing problems on maternal criticism[255].

4.3.4 Heritability of environmental phenotypes in adulthood

We know surprisingly little about the etiology of environmental phenotypes in adulthood. To date, there are no studies that have estimated the heritability of residing in deprived neighborhoods. A few studies have examined the heritability of residing in neighborhoods with other characteristics (e.g., urban settings and walkability) but the findings have been conflicting thus far[256-258]. A number of economists have used quantitative genetic models to estimate the heritability of long-term average earnings and the findings indicate substantial genetic influences[259-262].

Heritability estimates of phenotypes that measure different dimensions of socioeconomic status and residential characteristics could potentially be impacted by structural conditions in the society. As C.W. Mills noted, structural explanations of unemployment tend to be raised during periods of economic recession while individual explanations tend to be raised during periods of economic prosperity[263]. Sweden experienced a major economic recession in the early 1990s, which is illustrated by the unemployment rates in Figure 4.2.

Figure 4.2 Unemployment rate (percentages) in Sweden between 1985 and 2004



The question is whether this recession had an impact on the heritability estimates of adulthood likelihood to live in deprived neighborhoods, have low disposable income and to live in densely populated areas. To answer these questions, I examined all Swedish twins who were aged between 30-55 years at the baseline years of 1985 (n=39,538), 1990 (n=40,510), 1995 (n=40,220), 2000 (n=37,878) and 2005 (n=34,462) The participants were followed up for a period of 5 years and I calculated an average of their phenotypic scores. To account for non-linear effects, I generated binary measures of the phenotypes where those who scored in the 90th percentiles were coded as 1 and the rest as 0.

Figure 4.3 Etiology of low neighborhood deprivation

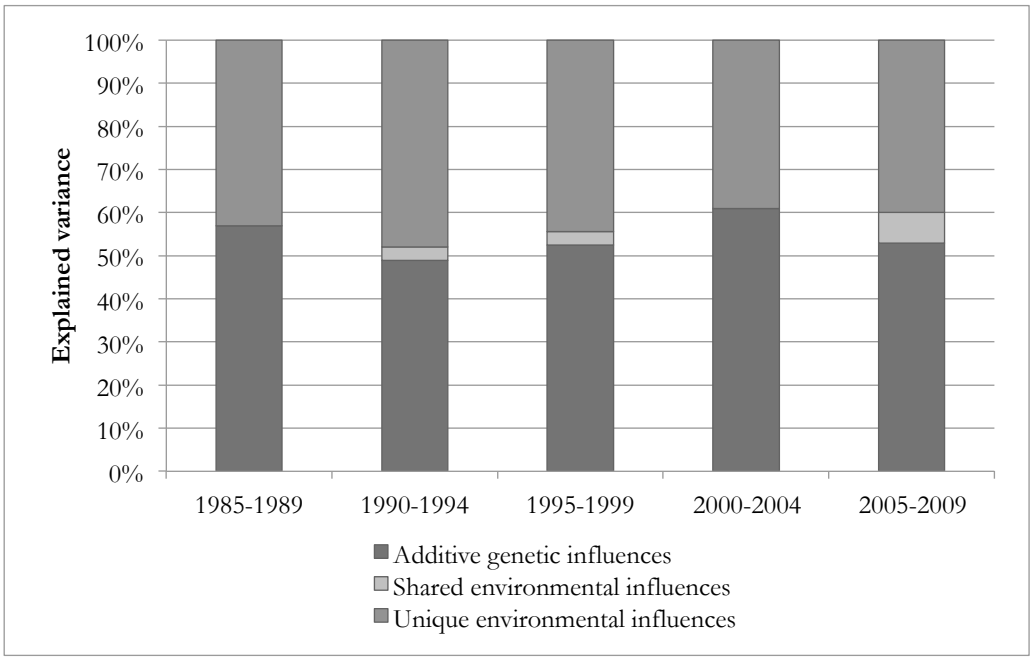


Figure 4.4 Etiology of low disposable income

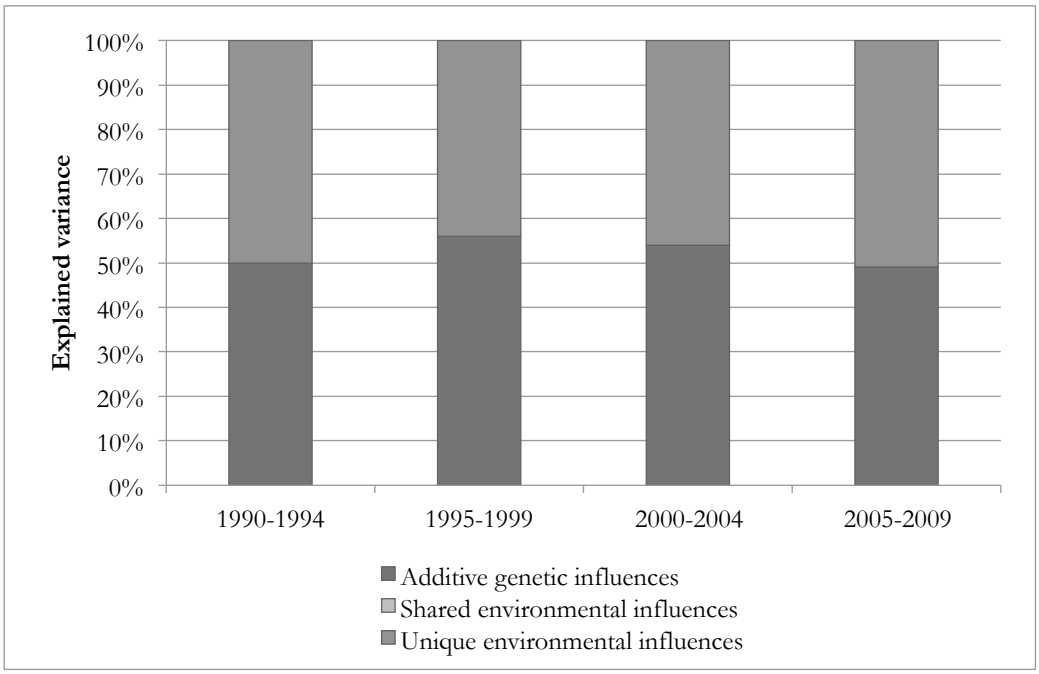
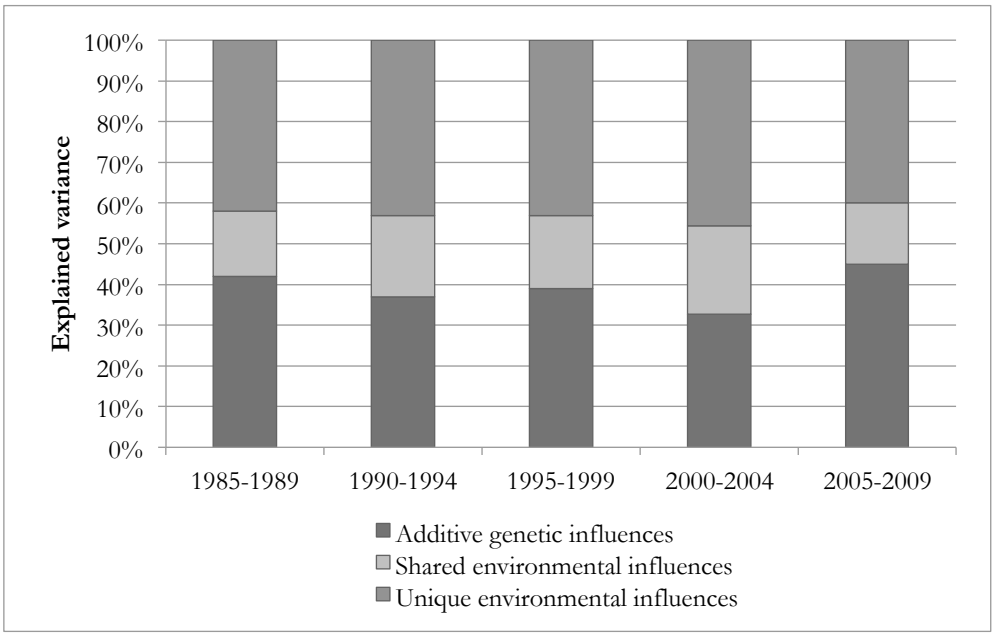


Figure 4.5 Etiology of high population density



The heritability estimates of all three phenotypes are remarkably stable across this turbulent economic period. Between 50 to 60 percent of the liabilities to reside in deprived neighborhoods and having low disposable income were explained by genetic factors (Figures 4.3 and 4.4). Furthermore, the shared environmental influences were very small in the case of neighborhood deprivation and essentially non-existent in the case of disposable income (Figures 4.3 and 4.4). The heritability estimates of living in densely populated areas were somewhat lower than those of the former phenotypes, fluctuating between 30-45 percent, and the shared environmental influences accounted for between 15-20 percent of the liabilities across time (Figures 4.5). These findings demonstrate why it is important to account for gene-environment correlations in social epidemiological studies.

4.3.5 The co-twin control design

Epidemiological research designs developed within the field of behavioral genetics nearly always deal with counterfactuals[221,264]. The co-twin control design is a popular approach that accounts for unobserved genetic and environmental confounds by comparing the risk for a given phenotype to occur between differentially exposed twins[265]. The connection between the co-twin control design and counterfactuals was made explicit in the introduction of the first publication using the approach, published in the late 1940s[266]:

> "[O]ne might like to train a child, and then compare him with what he would have been if he had not received the training. This cannot be done; there is no way to make the desired comparison. But we may study a pair of identical twins with just such comparisons in mind. We may train one twin (T) experimentally, and reserve the co-twin (C) as a control. C becomes a scientific kind of stand-in-double for T." (p. 446)[267]

If we conduct a standard non-experimental study, the differences observed between two exposure groups could potentially result from genetic and environmental differences (non-exchangeability). In the co-twin control design with MZ twins, however, the interest is generally to examine differences between MZ twins who have been reared together in the same family. It is therefore assumed that MZ twins share all of their co-segregating genes and their childhood family environments. The exchangeability between the twins, regardless of their exposure levels, is considered to be high as the differences between them can only be attributed to non-shared environmental influences[264,268].

4.3.6 Sibling-comparison designs

In the recent years, there has been an increasing interest among behavioral geneticists to extend the co-twin control design to the examination of differences between differentially exposed biological full-siblings[223,269,270]. This approach is often called the sibling-comparison design in behavioral genetics but economists have used the same model under the name of "sibling fixed-effects" for decades to study how childhood conditions affect long-term outcomes[271-273]. The classical twin studies attributed measures of childhood socioeconomic status (SES), including neighborhood residence, to the shared environmental component, namely to non-genetic factors that are shared within a family[274]. This assumption was necessary to make because the candidate environments did not differ between the twins, unless they were reared apart in rare instances[275]. Sibling-comparison designs, on the other hand, do not need to make the same assumption because non-twin full-siblings are born during different years, which imply that they will be exposed to different levels of SES during their upbringing at the same ages. For instance, two siblings who are born five years apart from one another will likely have different

exposures to parental income at birth because of the parents' career developments during the given time period.

The use of the sibling-comparison design to study early exposures to adverse SES conditions in the Swedish context is particularly informative due to the exogenous shock that the major economic recession in the early 1990s introduced. The recession worked as a natural experiment that generated downward social mobility for a large number of families at its genesis, which later turned into a process of upward social mobility for a proportion of those families during the recovery years. The strong exchangeability of siblings, who share half of their co-segregating genes as well as their home environment, could therefore be combined with considerable fluctuations in the families' economic conditions that were largely due to external market and policy factors.

The beauty of the sibling-comparison design lies in the fact that it can efficiently adjust for all time-constant factors that are shared by siblings without the need to incorporate them as measured covariates into the statistical model. However, there are a number of limitations to the approach that needs to be considered[223,270,276]:

External validity: An inherent assumption of the design is that differentially exposed full-siblings do not differ systematically from the general population in regards to the exposure and outcome of interest. The presence of such differences would essentially limit the external validity of the study to the sibling sub-sample, which is generally of little interest to the researchers. It is therefore important to consider the reasons for why the siblings have been differentially exposed.

Sample size: The design requires very large sample sizes because the only informative cases are families in which the siblings are differentially exposed to the exposure as well as the outcome. Depending on the prevalence and the overlap between the measures of interest, this can pose a problem even in nationwide registry studies. Larger sample sizes generally improve the external validity.

Measurement error: The design is particularly sensitive to measurement error and the derived estimates are therefore encumbered with lower levels of precision because of the fact that they only use data from a sub-sample of the population.

Non-shared environmental confounders: The design does not account for the influence of environmental factors that (a) correlate with the exposure and outcome and (b) is

not shared by all siblings in the family. Suppose that we want to study siblings that are differentially exposed to parental income in childhood on later violent criminality. An example of a non-shared environmental influence in this context would be traumatic brain injury (TBI)[277-280]. TBI has been found to be associated with low socioeconomic status[281-283] as well as with criminality[284-286]. If we were to observe, using a sibling-comparison model, that parental income predicted violent criminality, the findings could still be confounded by differential TBI exposure within the family. However, the sibling-comparison model is flexible enough to allow for the statistical adjustment of measured environmental factors that we believe confound the associations between the exposure and outcome beyond the unobserved familial confounders.

Non-shared genetic confounders: The design does only account for the genetic influences that are shared between siblings in a family. Residual genetic influences that make the same siblings dissimilar from one another could therefore confound the associations between the exposure and the outcomes.

Sibling independence assumptions: The design assumes, based on the foundations of the counterfactual framework that the treatment of one sibling should not impact the outcome of the other sibling. This assumption is referred to as the Stable Unit Treatment Value Assumption (SUTVA)[287] in the causal inference literature and "carry-over effects"[288,289] in the behavioral genetic literature. Returning to the example above, this assumption would imply, for instance, that the parental income exposure of the older sibling does not impact on the violent conviction outcome of the younger sibling. Another important assumption is the lack of "contagion effects", namely that the outcomes of both siblings are assumed to be independent (e.g., the older sibling cannot influence their younger sibling to engage in violent criminality)[289].

Comparing differentially exposed full-cousins offers an alternative quasi-experimental approach that can be used as a complementary tool to diagnose some of the limitations of the sibling-comparison design. Biological full-cousins only share 12.5 percent of their co-segregating genes and are assumed not to share their childhood environments. The latter environmental assumption may be violated in certain cultures where it is customary for extended families to live in the same household[290,291]. Commensurate findings between sibling and cousin-

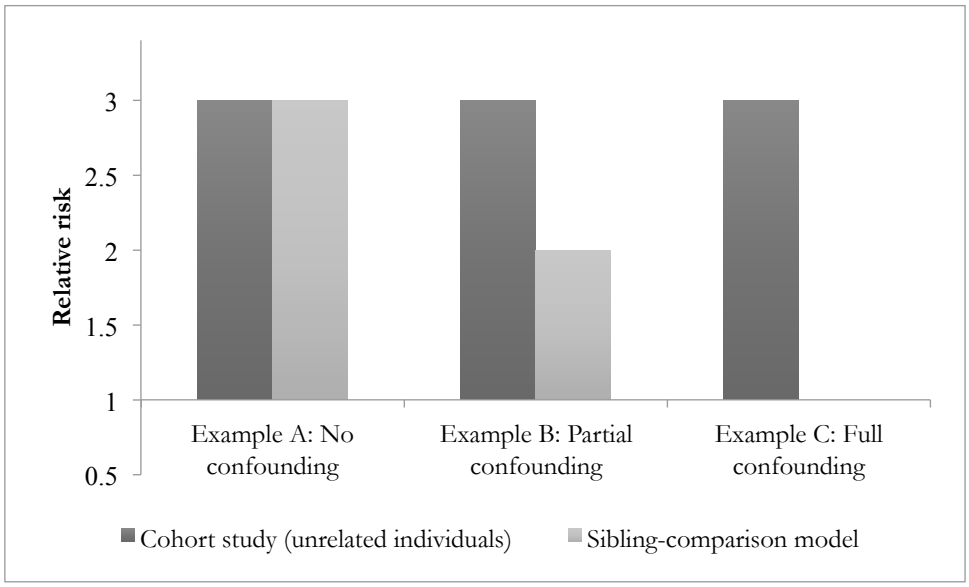
comparison models increase the external validity and relaxes the sibling independence assumptions described above.

4.3.6.1 Interpretation of sibling-comparison models

In nationwide registry studies employing sibling-comparison designs, the *modus operandi* generally involves comparing estimates derived from standard epidemiological approaches using unrelated individuals (e.g., cohort and case-control designs) with corresponding estimates derived from sibling-comparison models[292-294]. Because the former estimates ignore all factors that are constant within families (e.g., genes and home environments), they are often referred to as "between-family estimates". Sibling-comparison models, on the other hand, are only concerned with estimating differences between differentially exposed siblings within the same families, which is the reason for why such estimates are referred to as "within-family estimates". The relative magnitude of the unobserved familial confounders is normally measured as the difference between these two types of estimates.

Suppose that we are interested in understanding the causal nature of the association between being born in an urban area and subsequent risks of being diagnosed with schizophrenia. Let us also assume that both of these measures are binary in nature. We study this association in a large sample of unrelated individuals and observe that those who are born in urban areas are three times as likely as the controls to develop schizophrenia, which is reflected below in the relative risk of 3 in Figure 4.6 (Example A-C).

Figure 4.6 Examples of confounding patterns when comparing cohort and sibling-comparison studies



We then study biological full-siblings who are differentially exposed to urban birth and we fully replicate the previous finding, namely that in a family of two siblings, the one who was born in an urban area experienced a three-fold risk increase to develop schizophrenia as compared to their sibling who was born in a rural area (Example A). These findings suggest that the unobserved familial confounders shared within the families do not explain any of the excess risks that were measured in the population, as –the within-family estimate did not differ meaningfully from the between-family estimate. For this reason, we would assume that the results were consistent with a causal inference, if the model assumptions are otherwise met.

In Example B, however, we observe that the within-estimate is attenuated to a two-fold risk increase. This would imply that the unobserved familial confounds explain a portion of the association that was observed in the population, but not all of it. The residual effects are consistent with a causal inference, based on these findings. In Example C, we find a complete attenuation of the within-family effects, which implies that the unobserved familial confounds explain the entire association between being born in an urban area and later schizophrenia risk. The siblings in the study would have the same risk of developing schizophrenia within their families, regardless of the population density of their place of birth.

5 STATISTICAL MODELS

5.1 GENERALIZED LINEAR MODELS (GLM)

The linear regression model is commonly formulated as:

$$E(Y_i|x_i) = x_i^T\beta + \varepsilon_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \varepsilon_i, \quad \text{[Eq. 3]}$$

where $E(Y_i|x_i)$ is the expected value (e.g., mean) of the outcome measure (Y), given the included predictors in the model (x), for every *i*th observation. The betas (β) refer to regression coefficients and epsilon (ε) to the errors. The right-hand side of the formula is referred to as the linear predictor. While the linear regression model provides a powerful yet simple way of assessing linear associations between predictors and an outcome of interest, it is limited by its strong assumptions about the nature of the error terms, as outlined by the Gauss-Markov theorem[295]:

$$E(\varepsilon_i) = 0, i = 1, \ldots, N \quad \text{[Eq. 4]}$$

$$\mathrm{Cov}(\varepsilon_i, \varepsilon_j) = \begin{cases} \sigma^2 \text{ for } i = j \\ 0 \text{ for } i \neq j \end{cases} \quad \text{[Eq. 5]}$$

$$E(\varepsilon|X) = E(\varepsilon) = 0 \quad \text{[Eq. 6]}$$

$$\varepsilon_i \sim N(0, \sigma^2) \quad \text{[Eq. 7]}$$

The model assumes that the expected value of the errors is zero (Eq.4), implying that the predicted value should be, on average, correct. Furthermore, it assumes that the errors have same variance (Eq. 5), are uncorrelated with one another (Eq. 5) as well as with the predictors (Eq. 6). The errors are therefore assumed to be drawn from a normal distribution with a mean of zero and a constant variance (Eq. 7).

Discrete outcome measures (e.g., binary and counts), commonly adopted in epidemiology, often violate these assumptions. The generalized linear models (GLMs), developed in the early 1970s by Nelder and Wedderbaum[296], represented a new statistical framework in which the linear regression model was generalized to a broad range of alternative outcome distributions via the integration of the exponential family of distributions[297]. The GLM framework is interesting because

it keeps the simplicity of the linear model despite the non-linear transformation of the outcome. The GLM is formulated as follows:

$$g\big(E(Y_i|x_i)\big) = x_i^T\beta = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots, \qquad \text{[Eq. 8]}$$

where g(·) denotes the link function; a mathematical function describing that the expected value of the response is a function of the linear predictor. The GLMs employed in this dissertation have all adopted the logit link function for binary outcomes. Other link functions include identity (for continuous measures, equivalent to the linear regression model) and log (for counts using the Poisson distribution). Unlike the identity link function where the error term can be directly estimated, the logit link function specifies that the error term follow the logistic distribution, which has a mean of zero and a variance of $\frac{\pi^2}{3}$ or approximately 3.29[298].

The rationale for the logit model is to take a binary outcome measure and convert it to logarithm-transformed odds, referred to as log-odds or logits. The linear predictor is therefore assumed to be linearly associated with the outcome on the logit scale[299]. Suppose that we are interested in assessing the extent to which a predictor (e.g., gender, where 0 = female and 1 = male) is associated with a binary outcome (e.g., criminal conviction). The model would be formulated as follows:

$$E(Y_i|x_i) = \Pr(Y_i = 1|x_i)$$

$$\text{logit}\big(\Pr(Y_i = 1|x_i)\big) \equiv \ln\left(\frac{\Pr(Y_i=1|x_i)}{1-\Pr(Y_i=1|x_i)}\right) = \beta_0 + \beta_1 x_{i1} \qquad \text{[Eq. 9]}$$

The expected value of criminal conviction, Y_i, conditional on gender, x_i, for every *i*th individual is the probability that they are convicted (e.g., that the outcome equals 1). The odds of criminal conviction in each individual is defined as the ratio between the their probability of being convicted to their probability of not being convicted, conditional on their gender ($\Pr(Y_i=1 \mid x_i)/1-\Pr(Y_i=1 \mid x_i)$). The odds are subsequently ln-transformed to convert the scale of the outcome to logits. This model therefore enables us to assess the association between gender and criminal conviction on the logit scale. For instance, if we were to fit this model to a dataset and the derived effect size ($\widehat{\beta_1}$) was 1.5, we would interpret this as the log-odds of criminal conviction being 1.5 units higher in males as compared to females. This

estimate is, however, not intuitive to grasp and therefore not particularly informative. Instead, researchers tend to express effect sizes as odds ratios by exponentiating both sides of the equation[300]:

$$\exp\left[\ln\{\text{Odds}(Y_i = 1|x_i = a+1)\} - \ln\{\text{Odds}(Y_i = 1|x_i = a)\}\right] = \frac{\text{Odds}(Y_i=1|x_i=a+1)}{\text{Odds}(Y_i=1|x_i=a)} = \exp(\beta_1)$$

[Eq. 10]

In this specific case, the odds ratio (OR) of gender would be 4.48 (exp(1.5)=4.48), implying that the males in the sample experienced approximately a 4.5-fold increased odds of being convicted as compared to the females.

5.2 GENERALIZED LINEAR MIXED-EFFECTS MODELS (GLMM)

As was discussed in the previous section, the development of the GLMs addressed many of the violations of the Gauss-Markov theorem in situations where the outcome measure was discretely distributed. An important assumption that is not addressed by the GLMs is, however, that the observations are assumed to be independent, conditional on the included covariates. This assumption is violated in situations where individuals are non-randomly clustered into groups (e.g., neighborhoods, schools and families) that have not been accounted for by the model. Individuals in the same clusters will share numerous characteristics with one another that are not shared between individuals in different groups. The parameter estimates of a given model will be biased as a function of the extent to which such characteristics influence the exposure and outcome[301]. Simulation studies have demonstrated that neglecting clustered data structures may lead to severely downward biased standard errors of model parameters[302], which implies an increased risk of type I errors[74].

The statistical framework of generalized linear mixed-effect models (GLMMs), known as multilevel models in epidemiology[43,303], is often believed to constitute a viable solution to such limitations. The framework was introduced in the statistical literature in the mid-1980s[304-307] although its origins date back to the 1920s[37,308,309]. GLMMs extend GLMs by incorporating variance components that estimate the influences of complex data clustering. Applied neighborhood researchers often think that GLMMs are able to "tease out the effects of area[s] *independently* of the

characteristics of individuals" (p. 267, emphasis here)[94] but, as it will be demonstrated below, this is highly problematic in practice.

The logit GLMM is defined as follows:

$$\text{logit}\left(\Pr\left(Y_{ij} = 1 \middle| x_{ij}, z_{ij}\right)\right) = x_{ij}^T\beta + z_{ij}^T b_{ij} \quad \text{[Eq. 11]}$$

where the expected value of the outcome is conditional on a vector of covariates (x_{ij}) and variances (z_{ij}), respectively, across every *i*th cluster, for every *j*th individual. Although the exact terminology is far from clear[310], the models are called mixed because they combine fixed effects (e.g., expected values of the observations) with random effects (e.g., variances and covariances)[311]. The simplest form of a GLMM; "the empty model"[312], does not include any covariates but allows for the intercept to vary across a specified set of clusters. The covariance pattern is generally specified to take the form of "compound symmetry", which implies that the individual observations are assumed to be equally correlated within independent clusters[300].

Suppose, for instance, that we are interested in examining how neighborhood clustering impacts individual schizophrenia diagnosis. The empty model would be formulated as follows:

$$\text{logit}\left(\Pr\left(Y_{ij} = 1 \middle| z_{ij}\right)\right) = \beta_0 + b_i, \quad \text{[Eq. 12]}$$

$$b_i \sim N(0, \sigma_b^2) \quad \text{[Eq. 13]}$$

where b_i is the random effect for the varying intercepts across every *i*th neighborhood, for every *j*th individual (Eq. 12). The random effects are assumed to be independent and in most cases normally distributed (with a mean of zero and a constant variance; Eq. 13) in GLMMs but the framework is flexible enough to allow for alternative distributions as well[313]. The relative impact of neighborhoods on schizophrenia diagnosis can be expressed as an intraclass correlation (ICC)[41,43,312], which measures the relative degree of similarity between individuals residing in the same neighborhoods. The scale of the ICC measure ranges from 0 to 1, where the former indicates no within-neighborhood similarities in terms of

the studied outcome and the latter complete within-neighborhood similarities. One may alternatively interpret the ICC as the correlation between two randomly selected individuals in a given neighborhood[41]. The ICC is calculated as follows:

$$\mathrm{ICC} = \frac{\sigma_b^2}{(\sigma_b^2+\sigma_e^2)}\,, \qquad \text{[Eq. 14]}$$

where σ_b^2 is the cluster-level (e.g., neighborhood) variance and σ_e^2 the individual-level variance. GLMMs with logit link functions cannot directly estimate σ_e^2 but a common approximation is obtained by fixing σ_e^2 to the variance of the logistic distribution ($\frac{\pi^2}{3}$ or 3.29)[41,43,298,312]. Using Eq. 14 and assuming a neighborhood variance (σ_b^2) of 0.1, the ICC would be approximately 0.03. This would imply that 3 percent of the variance in individual schizophrenia diagnosis could be attributed to neighborhood influences.

It should be noted that the ICCs estimated using the logit link function are sensitive to the prevalence of the outcome measure and may therefore not be fully comparable across outcomes[314,315]. Alternative approaches to measuring clustering influences have therefore been proposed, including simulations[316] and measures that are only based on the neighborhood variation, such as the median odds ratio[43,314,317] and its marginal analogue; the pairwise odds ratio[318-320]. Moreover, GLMMs require sufficient statistical power in regards to the number of clusters to estimate accurate random effects; between 20-100 clusters are needed with the standard frequentist approaches while a smaller number of clusters may provide accurate estimates using Bayesian approaches[321-325]. Lastly, it has been recognized that older estimators for GLMMs, such as the (restricted) iterative generalized least squares ((R)IGLS)[326,327], estimate ICCs that are sensitive to small and/or varying cluster sizes[328,329]. These issues have nevertheless been resolved in newer and widely implemented estimators, such as the Gaussian adaptive quadrature[330-334].

5.2.1 General and specific neighborhood influences

In the epidemiological neighborhood literature, the ICC is conceptualized to capture "general neighborhood influences" or the relative relevance of neighborhoods as a social context for a given outcome of interest[335-337]. Once this effect size is known, the textbook rationale is to model for individual and

neighborhood-level covariates that may elucidate the underlying mechanisms explaining the observed variation between the neighborhoods[41,312]. This straightforward interpretation of GLMMs is unfortunately rather reductionistic, particularly in the case of neighborhood influences.

The independence assumption of unconditional GLMMs, namely that all individuals have an equal chance of residing in any neighborhood, implicitly assumes that any neighborhood clustering is causally related to the outcome because the random assignment would theoretically eliminate any confounding bias. In reality, however, it is recognized that individuals with similar characteristics select themselves into similar neighborhoods over time[338-340]. Neighborhood researchers have thus far only accounted for such selection factors by including measured covariates into GLMMs[18,52-57]. The residual variation between neighborhoods in regards to an outcome following statistical adjustments for measured covariates is assumed to be independent of individual-level influences. To explain such neighborhood variation, researchers commonly include specific neighborhood factors into the GLMMs, namely measures that oftentimes only vary between neighborhoods and therefore capture their aggregated social (e.g., neighborhood disadvantage[48,53,77,341], population density[51,60,61,171,172,342] and voter turnout[90,343,344]) and physical (air pollution[345,346], walkability[347-349], concentration of alcohol outlets[350,351]) characteristics.

The major limitation of this approach rests in its inability to accurately account for unobserved selection factors. The ”independent” general effects as well as the specific neighborhood influences could potentially result from familial confounds, as genetic and environmental influences shared within families explain at least half of the liability of residing in deprived Swedish neighborhoods in adulthood. This implies that individuals growing up in Sweden are non-randomly exposed to differential neighborhood conditions during their childhood and adolescence. It would seem rather implausible that only a set of observed measures would be able to account for such stark and complex influences.

5.2.2 Population average versus subject-specific estimates

GLMMs are computationally intensive to fit and make rather strong distributional assumptions in regards to the random effects and the relationship between the fixed and random effects. The cluster-robust sandwich estimator for GLMs is used

in situations where the primary interest rests in obtaining accurate standard errors for the fixed effects without the need to include random effects[352-355]. The cluster-robust estimator extends the Huber-White estimator[356,357] and uses the cluster-level variation as a nuisance parameter to constrain the error structure to compound symmetry.

It is important to recognize, however, that estimates derived from a GLM with cluster-robust standard errors are not equivalent to those derived from a GLMM[358]. In the former case, we are assuming that the mean effect of a given predictor is constant across the whole population, which is why they are referred to as population-average estimates. In the latter case, however, the average effect of a given predictor is conditional on the neighborhood of residence. Suppose that we add low-income status (0=no, 1=yes) as a predictor to the neighborhood-schizophrenia example above:

$$\text{logit}\big(\Pr\big(Y_{ij} = 1 \big| x_{ij}, z_{ij}\big)\big) = \beta_0 + \beta_1 x_{ij1} + b_i, \qquad \text{[Eq. 15]}$$

where x_{ij1} is the predictor and β_1 its regression coefficient across every *i*th neighborhood and *j*th individual. In this "random-intercepts model"[300], we are allowing the intercept (β_0) to vary across neighborhoods, captured by (b_i). The prediction of the effects of low-income status for each individual will therefore not only depend on whether or not they have low earnings but also on their neighborhood-specific intercept, which is why such estimates are referred to as subject-specific[314]. The main issue with subject-specific estimates is that they almost always violate a key assumption of the GLMM, namely that the fixed and random effects are uncorrelated[359]:

$$\text{Cov}\big(x_{ij}, z_{ij}\big) = 0 \qquad \text{[Eq. 16]}$$

In the context of this fictitious example, this implies that the low-income status is considered to be entirely unrelated to factors that make neighborhood residents more similar to one another in terms of their risks of being diagnosed with schizophrenia.

In the recent years, there has been an increasing interest in cross-classified GLMMs to simultaneously examine the relative importance of multiple clusters by including additional variance components[360-364]. The models are also referred to as

crossed random effects[300,332] or non-hierarchical models[365] in the literature. Earlier estimates of general neighborhood effects on adverse outcomes have been questioned in recent publications as the simultaneous adjustments for school-level clustering substantially or even entirely attenuate the previously observed neighborhood effects on a wide range of outcomes, including school marks[366], depressive symptoms[367], self-reported delinquency[368], and smoking[369]. A key issue in these types of models is the random effects are assumed to be independent from one another. The factors that make the study participants who live in the same neighborhoods more similar to one another are therefore assumed to be unrelated to the factors that make students in the same schools similar to one another in terms of the outcome of interest.

5.2.3 Between-within decomposition

The covariate effects derived from GLMMs are implicitly assumed to be equal between as well as within the specified clusters[370]. For instance, if we fit a GLMM clustered on families (siblings) that examines the association between low-income status and violent crime, we are assuming that the effect of low-income is the same between and within the families. The between-within decomposition parameterization[370], also known as the Mundlak approach in econometrics[371,372], allows us to disentangle such covariate effects appropriately by including a measure of the average exposure score ($\bar{x}_i$) for every family in addition to the individual sibling difference from mean (x_{ij1}):

$$\text{logit}\left(\Pr\left(Y_{ij} = 1 \middle| x_{ij}, z_{ij}\right)\right) = \beta_0 + \beta_1 x_{ij1} + \beta_2 \bar{x}_i + b_i, \qquad \text{[Eq. 17]}$$

The estimated β_1 will therefore capture the within-family effects while β_2 the between-family effects. If there are no systematic differences between the sibling sub-sample and the total population, one expects β_2 to corresponds to the crude population effect between the exposure and outcome. It is important to note that the β_1 only uses information from families where the siblings are differentially exposed because it relies on individual differences from the family averages; siblings that have the equivalent exposures can only contribute to the other model parameters (β_2 and b_i). The between-within parameterization does not, however, eliminate the distributional assumptions that are made by the GLMM framework[373].

The fixed-effects model is an alternative approach that differences away all of the between-family variation and only retains the within-family effects[374,375]. The strengths of this approach include that it is very computationally efficient and makes fewer distributional assumptions than GLMMs (e.g., since no random effects are modeled for, we do not need to consider correlations between fixed and random effects, as well as between random effects). The list of limitations include that it does not provide estimates of the clustering effects and that the reliance on differentially exposed siblings decreases the informative sample size, which in turn increases measurement error.

5.3 COX REGRESSION

The Cox regression model, formulated by Sir David Cox in the early 1970s[376], is a semi-parametric approach to modeling survival or "time-to-event" data[377,378]. Survival models are not only concerned with measuring the risk for an event to occur but also the amount of time it takes for it to occur. They additionally account for right censoring, namely that study participants leave the study prior to the occurrence of the event or the end of the end of the follow-up period. The Cox regression model is defined as follows:

$$\lambda(t|X) = \lambda_0(t)\exp(\beta X), \qquad \text{[Eq. 18]}$$

where λ is the hazard rate or the instantaneous risk for the event to occur at a given time point (t), conditional on the covariates, X. The model does not have an intercept like GLMs but a baseline hazard function $\lambda_0(t)$ that is not estimated but assumed to be an arbitrary function of time. The model estimates relative hazard rates across the specified covariates and the magnitude of the effects is generally expressed as hazard ratios (HR). The model is referred to as semi-parametric because it does not make any parametric assumptions about the baseline hazard function but only assumes that the hazard rates are proportional.

The Cox model can include random effects in so called frailty models but estimations of such models are computationally intensive and generally slower than GLMMs[378,379]. The stratified Cox model allows for the estimation of separate baseline hazards across different strata (e.g., families), which provides within-stratum estimates analogous to within-cluster estimates in fixed-effects models.

5.4 QUANTITATIVE GENETIC MODELS

5.4.1 The classical twin model

Quantitative genetic models are primarily concerned with the decomposition of phenotypic variation into genetic and environmental influences. The classical twin

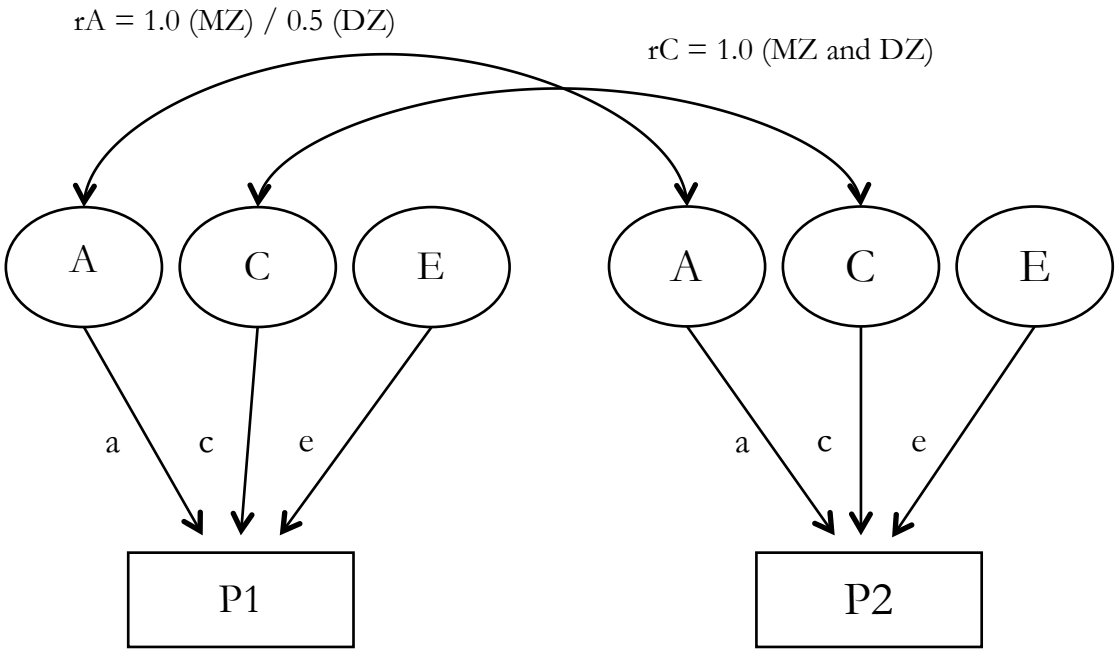
model, for instance, decomposes the variation of a given trait into three distinct components; additive genetic influences (A), shared environmental influences (C) and unique environmental influences (E). The latter component additionally captures the remaining measurement error.

$$\sigma_P^2 = \sigma_A^2 + \sigma_C^2 + \sigma_E^2$$

This particular specification of the twin model produces what is termed a narrow-sense heritability (e.g., heritability based solely on the additive genetic effects) estimate as it ignores potential genetic interaction effects within (*dominance*) and between (*epistasis*) loci[228]. The classical twin model is unable to simultaneously estimate additive and interaction effects due to the negative degrees of freedom it would entail[380]. It is, however, possible to adopt more complex models to estimate such effects but a recent simulation study indicated that narrow-sense heritability estimates are not meaningfully different from broad-sense heritability estimates that take such interactions into account[381].

Quantitative genetic models have traditionally been implemented within the structural equation modeling framework (SEM)[382], where the sources of genetic and environmental influences to the phenotypic variance are estimated as continuous latent variables[225]. It is nevertheless possible to fit equivalent models using the GLMM framework with additional specification of covariance constraints[383-385]. The latent variables would in the GLMM framework correspond to additional random effects[386]. Figure 5.1 below is a path diagram illustrating the classical twin model as a SEM.

Figure 5.1 The classical twin model as a path diagram



The rectangular boxes (P1 and P2) refer to the phenotypic score of each twin 1 and 2 in each family while the circles refer to the latent variables (or variance components) that measure the relative influences of genetic (A) and environmental (C and E) contributions to the etiology of the phenotype (P). The standardized regression coefficients (a, c, and e) reflect the magnitude of the associations between the latent variables and the phenotypes. The latent variables are assumed to be standardized and independent, which implies that the model does not account for any potential gene-environment interplay. MZ twins are assumed to share all of their co-segregating genes, which is why their correlation in the A latent variable (rA) is 1.0. DZ twins are assumed to share half of their co-segregating genes so their correlation in the A latent variable is 0.5. Both MZ and DZ twins are assumed to share their childhood environments and will therefore be perfectly correlated on the C latent variable (rC=1.0). The E latent variables are not correlated as they measure factors that are unique to each individual twin in the family.

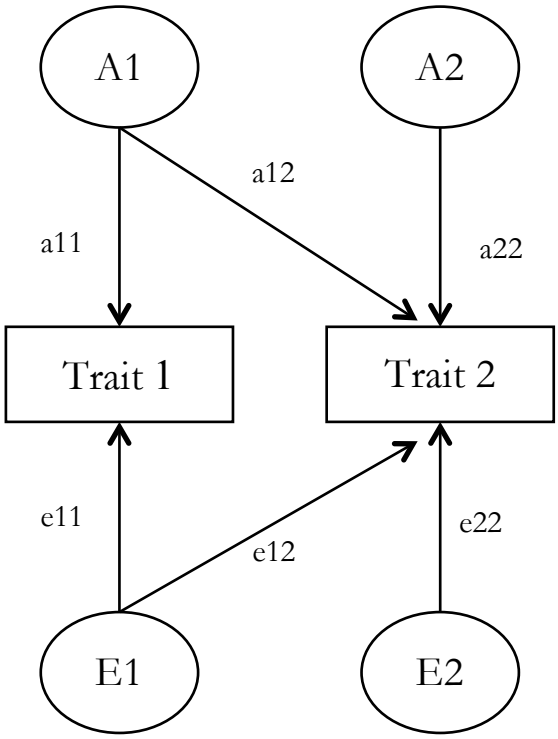
The classical twin model can be extended in a number of ways:

- Categorical phenotypes may be modeled under the liability-threshold model, which corresponds to the standard GLM assumptions.
- Multivariate models to account for multiple phenotypes.
- Covariates, called definition variables, such as sex and age, can be added to to account for differential average group differences in the population.
- Moderators of A, C and E (e.g., to examine heritability-environment interactions) can also be incorporated[387,388].
- Other sibling types can be added to increase the statistical power and the external validity of the findings with the following assumptions[88,89,225]:
    - Full-siblings (rA=.5; rC=1.0),
    - Maternal half-siblings (rA=0.25; rC=1.0) and
    - Paternal half-siblings (rA=0.25; rC=0).

5.4.2 Bivariate models

An important extension of the classical twin model is the possibility of accounting for genetic and environmental influences in the overlap between multiple phenotypes. The Cholesky decomposition approach is one of many multivariate parameterizations that enable the researcher to estimate the phenotypic correlations between traits as well as the genetic and environmental contributions to the correlations. Figure 5.2 below demonstrates the decomposition approach in the bivariate case as a path diagram.

Figure 5.2 Bivariate Cholesky decomposition as a path diagram



A1 measures the additive genetic contributions to the first trait (Trait 1), the strength of which is measured by a11. However, A1 does also load on the second trait (a12) to be able to estimate the genetic overlap between both traits. A2 will thereafter capture any residual genetic influences that are unique to that specific trait. The same logic applies to E1 and E2 (as well as e11, e12 and e22).

The phenotypic correlation (rPh) between Trait 1 and Trait 2 is calculated as follows: (a11*a12)+(e11*e12). We may thereafter also calculate the relative contributions of additive genetic influences ((a11*a12) /rPh) and unique environmental influences ((e11*e12) /rPh).

6 STUDY SUMMARIES AND RESULTS

6.1 STUDY I – NEIGHBORHOODS ON VIOLENCE AND SUBSTANCE MISUSE

Study I is a prospective cohort study where we examined general neighborhood effects as well as the specific effects of neighborhood deprivation on violent criminality and substance misuse during adolescence after adjustments for unobserved familial confounders.

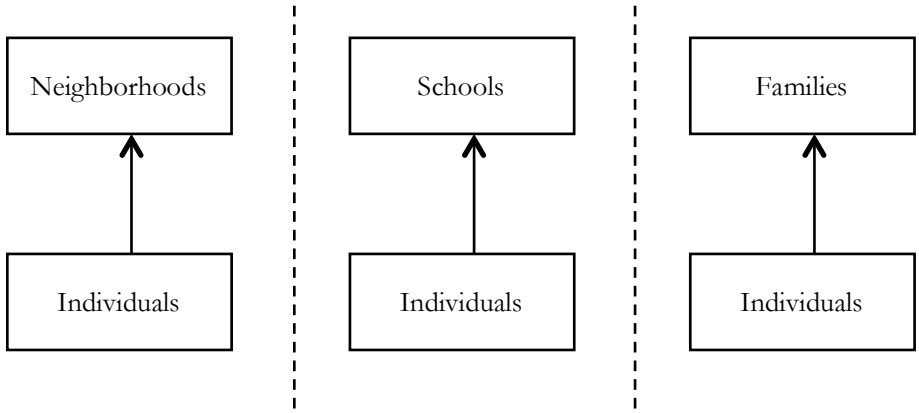
Using the MBR, we identified a sample of individuals who had been born in Sweden between 1975 and 1989 (n=1,475,147). We excluded children who had missing data on birth characteristics (n=36,731), biological parents (n=14,048) and parental socioeconomic status measures (n=44,676). Individuals who did not attend primary schools with at least 50 students (n=47) or who did not reside in metropolitan areas (n=1,034,520) at the end of the year they turned 15 years of age were further excluded. We defined metropolitan areas as SAMS communities with at least 500 residents located within and in proximity of the three largest cities of the country (Stockholm, Gothenburg and Malmö). The final sample consisted therefore of 297,752 study participants. In a separate dataset, we identified and retained all of the biological full-siblings in the sample, which included a total of 172,525 participants.

Violent criminality was defined as a violent crime conviction registered in the NCR between ages 15 and 20 years. In a similar way, we defined substance misuse as a criminal conviction for any crimes involving either alcohol or illicit substances or being diagnosed with an alcohol or substance-related diagnosis in the NPR. We utilized the broad definition of the neighborhood deprivation measure and included the following confounders: sex, birth year, birth order, small or large for gestational age, immigrant descent, primary school grade point average, parental income, welfare recipiency, education level, single-parent household, residential mobility and parental criminal convictions and substance misuse.

We estimated crude ICCs to investigate how much of the variance in violent crime and substance misuse that could be attributed to the neighborhood, school and family contexts, respectively, by fitting a total of six separate GLMMs with a logit link function and random intercepts for the SAMS neighborhoods on the total

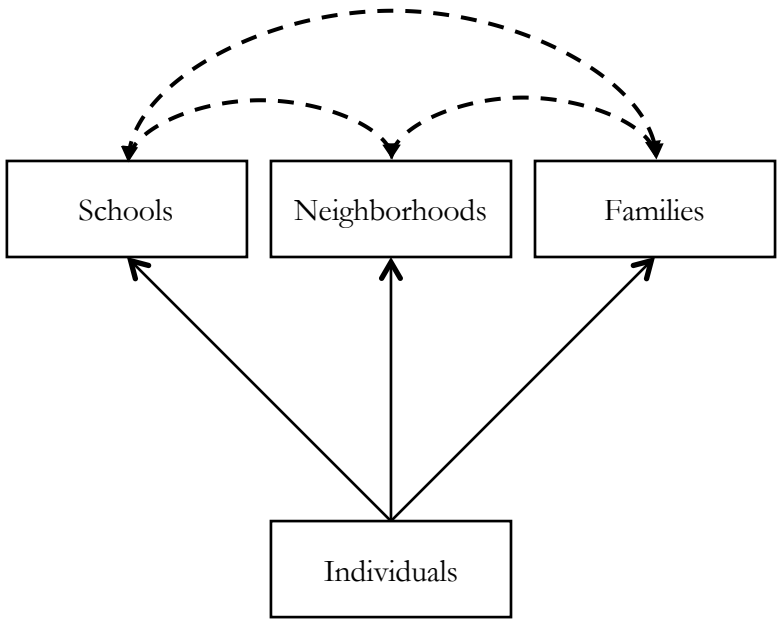
population dataset. Figure 6.1 below illustrates the nested data structures of the models for each outcome measure.

Figure 6.1 Graphical representation of the nested data structure in the crude models



The adjusted ICCs were derived from two separate cross-classified GLMMs fitted for each outcome measure, where we simultaneously modeled for all three contexts and included the measured confounders. Figure 6.2 below illustrates the cross-classified data structure of the models.

Figure 6.2 Graphical representation of the cross-classified data structure in the adjusted models



The arrows in the bottom part of Figure 6.2 indicate that the cross-classified model takes into account that the study participants are simultaneously clustered within neighborhoods, schools and families. The arrows in the top part of the same figure indicate that the model additionally accounts for the fact that not all family members lived in the same neighborhoods at age 15 years or attended the same primary schools and that unrelated participants who lived in the same neighborhoods did not necessarily attend the same primary schools.

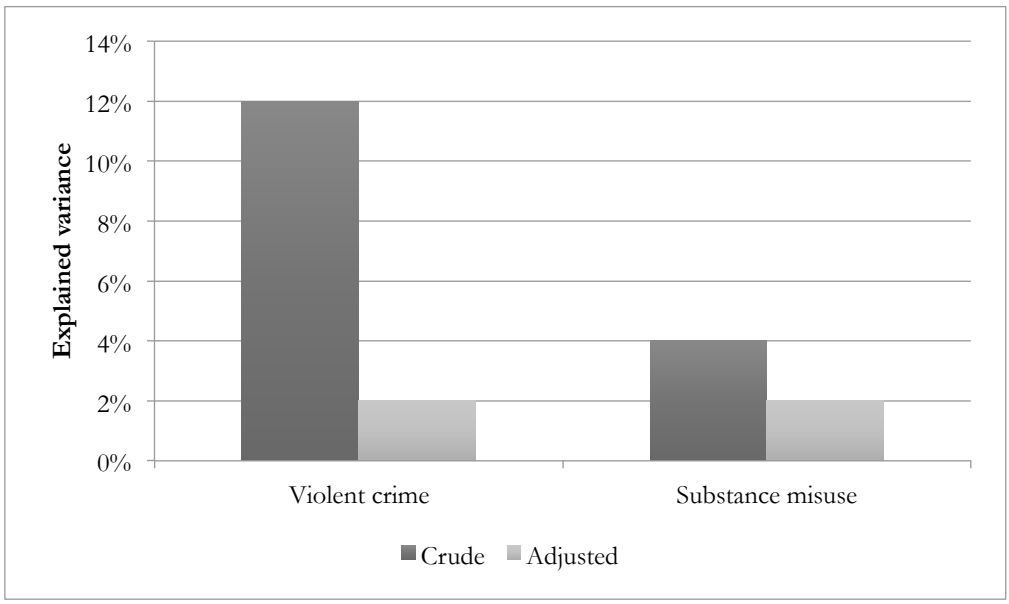
To study the specific effects of neighborhood deprivation, we fitted a series of GLMMs that gradually accounted for confounding factors. The crude model was a GLMM with a logit link function and a random intercept for neighborhoods that only included the exposure as a covariate. This model was fitted on the full sample. The adjusted model was fitted on the sibling sub-sample and included two additional random intercepts for schools and families as well as the measured confounders. The final within-sibling model combined the cross-classified GLMM approach with the between-within parameterization of the neighborhood deprivation exposure, which allowed us to explicitly study whether differences in neighborhood deprivation exposure within families, between siblings, predicted the outcomes.

6.1.1 Results

6.1.1.1 General neighborhood effects

The crude general neighborhood effects explained 12 percent of the variance in violent criminality and 4 percent of the variance in substance misuse (Figure 6.3). In the adjusted model, where we additionally accounted for clustering by schools and families as well as a wide range of confounding factors, the estimates were substantially attenuated; neighborhoods only accounted for 2 percent of the variance in both violent criminality and substance misuse.

Figure 6.3 General neighborhood effects on violent criminality and substance misuse



6.1.1.2 Specific effects of neighborhood deprivation

In the total population sample, we found that a standard deviation increase of the neighborhood deprivation score was associated with almost a 60 percent increased odds of being convicted of a violent crime (Table 6.1). Although substantially attenuated, the effects persisted in the model that adjusted for the cross-classified clustering and the measured confounding factors; an SD increase of the neighborhood deprivation score was now associated with a 9 percent increased odds of being convicted of a violent crime. In the final model, where we compared differentially exposed siblings, we found that the association was fully attenuated; siblings who had been exposed to higher levels of neighborhood deprivation did not experience any increased risk of being convicted of violent offences compared to their siblings who had been exposed to lower levels of neighborhood deprivation.

The associations between neighborhood deprivation and substance misuse were smaller in magnitude. In the crude model, one standard deviation increase in the neighborhood deprivation score was associated with approximately 30 percent increased odds of engaging in substance misuse. This association was, however, fully attenuated when we accounted for the cross-classified data structure and the measured confounders. The within-sibling analyses confirmed the adjusted model;

siblings who had been exposed to higher levels of neighborhood deprivation compared to their siblings did not experience higher odds of engaging in substance misuse.

Table 6.1 Specific effects of neighborhood deprivation on violent criminality and substance misuse

	Violent crime **OR [95% CI]**	**Substance misuse** **OR [95% CI]**
Crude	1.57 [1.52; 1.63]	1.31 [1.28; 1.35]
Adjusted	1.09 [1.06; 1.12]	0.98 [0.96; 1.01]
Within-sibling adjusted	0.96 [0.83; 1.11]	1.05 [0.93; 1.19]

6.2 STUDY II – FAMILY INCOME ON VIOLENCE AND SUBSTANCE MISUSE

Study II is a prospective cohort study where we examined whether childhood family income predicted individual propensity to engage in violent criminality and substance misuse during adolescence after adjustments for unobserved familial confounders.

We initially included all children born in Sweden between 1989 and 1993 as identified via MBR (n=594,127) and set the following exclusion criteria: multiple births (n=14,670), serious malfunctions at birth (n=20,905), no data on both biological parents (n=3,956), died (n=2,526) or migrated (n=18,301) before the age of 15 years and missing data on parental socioeconomic status measures (n=7,603). We were therefore able to retain almost 89 percent of the targeted sample (n=526,167). To account for familial confounders, we additionally generated two sub-samples of all identified biological cousins (n=262,267) and full-siblings (n=216,424) in the sample.

The study participants entered the study on their 15th birthday and were up until they either experienced the outcome of interest (e.g., violent crime conviction or substance misuse conviction/diagnosis), migrated or died until 31 December 2009, whichever occurred first. The average follow-up time was 3.5 years with a maximum of 6 years, which implies that the oldest participants were 21 years of age at the end of the follow-up.

We estimated hazard ratios with 95 percent confidence intervals by fitting Cox regression models to assess the associations between childhood family income and the outcomes of interest. We fitted two statistical models on the total population sample that gradually accounted for measured confounders. Model I adjusted for sex, birth year and birth order while Model II additionally adjusted for the following parental measures; highest achieved education, age at birth of the first offspring and any history of mental disorders.

We fitted stratified Cox regression models to estimate whether differences within families predicted the outcomes of interest. Model III was therefore only fitted on the cousin sub-sample and we allowed for the estimation of different baseline hazards across extended families to account for unobserved familial risk factors shared by cousins (12.5% of their co-segregating genes) in addition to the same set

of covariates adjusted for in Model II. The final model, Model IV, was fitted on the full-sibling sub-sample and we allowed for the estimation of different baseline hazards across nuclear families to account for unobserved familial risk factors shared by siblings (50% genes, 100% shared environment).

6.2.1 Results

Children who grew up in households where the family income ranked in the bottom quintile of the population experienced an almost seven-fold increased risk of being convicted of a violent offence compared to their peers who grew up in households where the family income was ranked in the top quintile (HR=6.78; Model I in Table 6.2). When we account for measured parental confounders, the estimate was reduced to a four-fold increased risk (HR=3.93; Model II). Surprisingly, we found that the estimate was halved when we accounted for unobserved confounders shared by cousins (HR=1.89; Model III). In the final sibling-comparison model, the effect ceased to persist; siblings who were differentially exposed to different levels of childhood family income levels did not differ from one another in terms of their risks of being convicted of violent offences.

Table 6.2 Relative risks for violent crime as a function of childhood (ages 1-15) family income by quintiles.

	Model I	**Model II**	**Model III**	**Model IV**
	HR [95% CI]	**HR [95% CI]**	**HR [95% CI]**	**HR [95% CI]**
Quintile 1 (low)	6.78 [6.23; 7.38]	3.93 [3.59; 4.30]	1.89 [1.40; 2.56]	0.95 [0.44; 2.03]
Quintile 2	3.66 [3.35; 4.00]	2.50 [2.28; 2.74]	1.46 [1.09; 1.95]	0.81 [0.41; 1.61]
Quintile 3	2.14 [1.95; 2.36]	1.61 [1.46; 1.77]	1.04 [0.78; 1.40]	0.76 [0.42; 1.39]
Quintile 4	1.64 [1.48; 1.81]	1.34 [1.21; 1.48]	0.80 [0.60; 1.06]	0.64 [0.39; 1.05]
Quintile 5 (high)	Reference	Reference	Reference	Reference

We observed a similar pattern of effects, albeit with substantially lower effect sizes, when we examined substance misuse as outcome. Children in the lowest family income quintile experienced a 2.5-fold increased risk of engaging in substance misuse compared to their peers in the top income quintile (HR=2.45; Model I in Table 6.3). Accounting for measured parental confounders attenuated the estimate to a 2-fold increased risk (HR=1.98; Model II), which was almost halved when we studied differentially exposed cousins (HR=1.53; Model III) and ceased to persist when we studied differentially exposed full-siblings (1.11; 95% CI: 0.62; 1.98; Model IV).

Table 6.3 Relative risks for violent crime as a function of childhood (ages 1-15) family income by quintiles.

	Model I **HR [95% CI]**	**Model II** **HR [95% CI]**	**Model III** **HR [95% CI]**	**Model IV** **HR [95% CI]**
Quintile 1 (low)	6.78 [6.23; 7.38]	3.93 [3.59; 4.30]	1.89 [1.40; 2.56]	0.95 [0.44; 2.03]
Quintile 2	3.66 [3.35; 4.00]	2.50 [2.28; 2.74]	1.46 [1.09; 1.95]	0.81 [0.41; 1.61]
Quintile 3	2.14 [1.95; 2.36]	1.61 [1	1.04 [0.78; 1.40]	0.76 [0.42; 1.39]
Quintile 4	1.64 [1.48; 1.81]	1.34 [1.21; 1.48]	0.80 [0.60; 1.06]	0.64 [0.39; 1.05]
Quintile 5 (high)	Reference	Reference	Reference	Reference

6.2.1.1 Income correlations within families and measurement error

In a traditional cohort study, the extensive exposure period of 15 years for the family income measure reduces the risk of misclassification bias. A shorter exposure period may, for instance, capture a family who is only temporarily undergoing economic hardships. The longer exposure period becomes, however, a problem in a within-family context because it makes the relatives more similar to one another, which in turn increases the measurement error and the precision of our within-family estimates. For instance, the correlation between siblings in terms of the exposure measuring family income between ages 1-15 years was 0.98. This implies that only 2 percent of the variability in family income is unique to each offspring. To address this issue, we generated alternative exposure definitions ranging from five-year age bands to one-year age bands. Sibling correlations for the

former were still very high (e.g., above 0.9) but reasonable for the latter (ranging between 0.57 and 0.74). When we re-ran Model I-IV using these alternative exposure definitions, we found negligible differences from the presented findings, which strengthens our final conclusions.

6.3 STUDY III – NEIGHBORHOODS ON SCHIZOPHRENIA

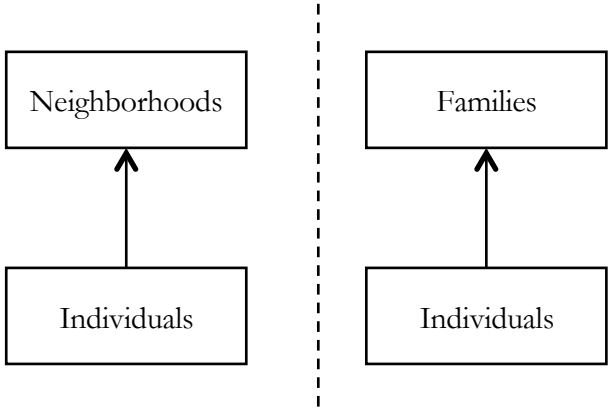
Study III is a prospective cohort study where we examined general neighborhood effects as well as the specific effects of population density and neighborhood deprivation on the risk of developing schizophrenia while adjusting for unobserved familial confounders.

The base sample consisted of all individuals who were born between 1967 and 1989, could be linked to both of their biological parents and had resided in Sweden at some point up until the end of 2009 (n=2,530,788). We set the following exclusion criteria: died (n=23,359), migrated (n=116,998), diagnosed with schizophrenia (n=72) or depression (n=1,121) prior to the age of 16 years as well as having incomplete data on residential area (n=25,173) or living in a residential area with less than 50 inhabitants (n=2,480). We were able to retain over 93 percent of the base sample (n=2,361,585). To account for familial confounders, we additionally generated two sub-samples of all identified biological cousins (n=1,715,059) and full-siblings (n=1,667,894) in the sample.

The neighborhood exposures were measured at the end of the year the study participants had turned 15 years of age. The study participants entered the study on their 15th birthday and were up until they were diagnosed with schizophrenia, migrated or died until 31 December 2009, whichever occurred first. The median follow-up time was 16.5 years with a maximum of 27 years, which implies that the oldest participants were 42 years of age at the end of the follow-up.

We estimated crude ICCs to investigate how much of the population variance in schizophrenia that could be attributed to the neighborhood and family contexts, respectively, by fitting a total of two separate GLMMs with a logit link function and random intercepts for the contexts on the total population dataset. Figure 6.4 below illustrates the nested data structures of the models.

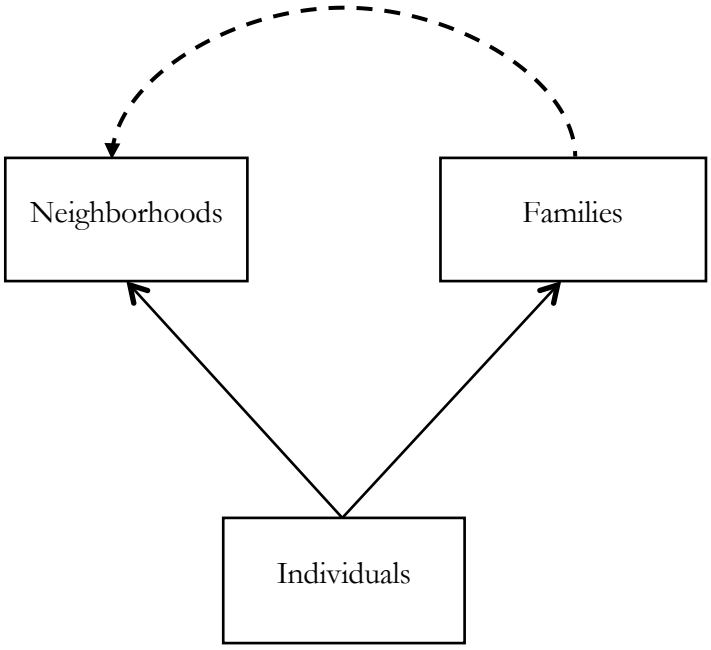
Figure 6.4 Graphical representation of the nested data structure in the crude models



We derived adjusted ICCs for neighborhoods and families by fitting a cross-classified GLMM on a sample of siblings who lived in different neighborhoods at 15 years of age. This approach allowed us to explicitly assess the extent to which unrelated individuals who were exposed to the same neighborhoods shared any characteristics that increased their likelihood of developing schizophrenia. Figure 8.5 below illustrates the cross-classified data structure of the model.

We estimated odds ratios with 95 percent confidence intervals by fitting a series of logistic regression models to assess the associations between population density, neighborhood deprivation and subsequent schizophrenia. Conditional logistic regression models were fitted to assess within-family effects, or the extent to which differences between differentially exposed cousins and siblings predicted schizophrenia. Identifiers for extended and nuclear families, respectively, were used to define the strata.

Figure 6.5 Graphical representation of the cross-classified data structure in the adjusted models



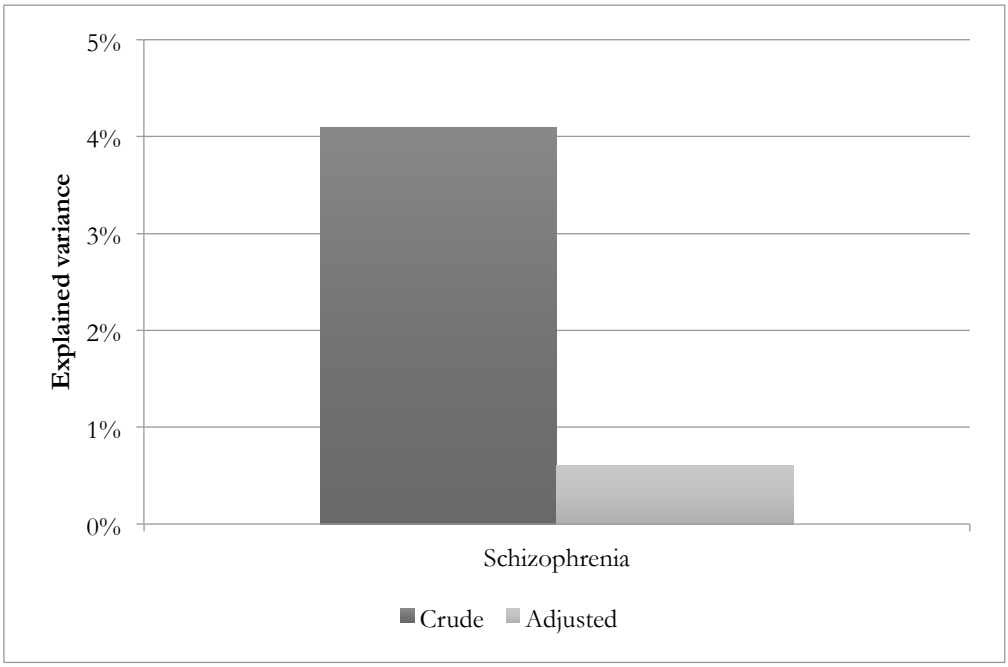
The crude model, Model I, was fitted on the total population sample and adjusted for sex, birth year and birth order. Model II was fitted on the cousin sub-sample and additionally accounted for unobserved familial confounders shared by differentially exposed cousins. Model III was fitted on the sibling sub-sample and similarly accounted for unobserved familial confounders shared by differentially exposed full-siblings.

6.3.1 Results

6.3.1.1 General neighborhood effects

The crude general neighborhood effects explained 4 percent of the variance in schizophrenia (Figure 6.6). This estimate was, however, fully attenuated in the adjusted model, where we additionally accounted for clustering by families. The point estimate was not significantly different from zero (ICC=0.006; 95% CI: 0.000-0.021). This implies that unrelated individuals who grew up in the same neighborhoods did not share any characteristics that increased their likelihood of developing schizophrenia.

Figure 6.6 General neighborhood effects on schizophrenia



6.3.1.2 Specific effects of population density and neighborhood deprivation

We initially tested whether continuous measures of our exposure variables predicted schizophrenia (Table 6.4). In the population (Model I), we observed that a percentage unit increase in population density was associated with a 10 percent increased odds of being diagnosed with schizophrenia. In Model II, where we additionally accounted for unobserved familial confounders shared by differentially exposed cousins, we observed that the estimate was reduced to 6 percent. The effects were fully attenuated in Model III, where we further accounted for unobserved familial confounders shared by differentially exposed full-siblings. The same pattern of effects were observed for neighborhood deprivation as exposure; a standard deviation unit increase of the deprivation score was associated with 43 percent increased odds of schizophrenia (Model I), which was halved in cousin-comparison model (Model II) and fully attenuated in the sibling-comparison model (Model III). Siblings who grew up in different neighborhood environments in regards to population density and socioeconomic deprivation did not differ from one another in terms of their risks to develop schizophrenia.

Table 6.4 Odds ratios (ORs) with 95% confidence intervals (CI) for schizophrenia as a function of continuous measures of population density and neighborhood deprivation at 15 years of age.

	Model I OR [95% CI]	Model II OR [95% CI]	Model III OR [95% CI]
Population density	1.10 [1.09; 1.11]	1.06 [1.03; 1.10]	1.02 [0.97; 1.08]
Neighborhood deprivation	1.43 [1.38; 1.49]	1.19 [1.07; 1.33]	1.01 [0.89; 1.16]

6.3.1.3 Extensive sensitivity tests

Given the strong links identified between these exposures and schizophrenia in the literature, we decided to run an extensive set of sensitivity analyses to rule out any potential alternative explanations as to our null findings within families:

- Categorical definitions of the exposures (e.g., tertiles and quintiles)
- Alternative definitions of schizophrenia (one episode only, in-patient care)
- Timing and accummulation impact of the exposures (mean scores and age categories from birth up to age 15 years)
- Alternative model paramaeterizations, including Cox regression models to account for time at risk and fixed-effects models to remove random effects assumptions
- Sub-samples based on sex, nationality and family composition

We found that the pattern of effects observed in the main findings was fully replicated in the sensitivity analyses.

6.4 STUDY IV – ETIOLOGY OF SOCIAL DRIFT IN SCHIZOPHRENIA

Study IV is a bivariate quantitative genetic sibling study using prospective cohort data where we were interested in examining the etiology of the social drift hypothesis for schizophrenia, including estimating the relative contributions of genes and environments. The drift hypothesis postulates that schizophrenia patients, due to their illness, gradually drift downward in the social hierarchy. Living in deprived neighborhoods is therefore viewed as being a consequence rather than a cause of the disorder. We used the TCHAD dataset to replicate our findings using subclinical measures of psychotic experiences as well.

The base sample in the sibling study consisted of all individuals who were born between 1951 and 1974 and could be linked to both of their biological parents (n=2,628,631). Individuals who had either died (n=41,440) or migrated (n=163,868) prior to the age of 35 years were excluded as well as those who lacked data on their place of residence between ages 31 and 35 years (n=37,315). We were therefore able to retain a sample of 2,386,008 individuals (90.8 percent) of those included in the base sample. Following the identification of all full and half-siblings in this sample, we decided to only retain the oldest two siblings in each family who were born a maximum of five years apart from one another to accommodate the shared environment assumption. In the final analyses, we had included a total of 759,536 full-sibling pairs, 68,684 maternal half-sibling pairs and 82,913 paternal half-sibling pairs.

Our exposure consisted of a binary indicator of whether the participant had been hospitalized for a diagnosis of schizophrenia on at least two occasions prior to the age of 31 years. The outcome was a binary measure of whether the participant had ever lived in a deprived neighborhood between ages 31 and 35, defined as the 95th percentile of the continuous distribution.

In the TCHAD replication twin study, the exposure variable consisted of parent-reported psychotic experiences (auditory hallucinations) between ages 8-17 years. The outcome was a binary measure of whether the participant had ever lived in a deprived neighborhood between ages 23 and 24, defined as the 75th percentile of the continuous distribution.

Our initial analyses consisted of univariate quantitative genetic models, where we fixed the genetic correlation for the full and half-siblings to 0.5 and 0.25, respectively. The shared environmental correlation was set to 1.0 for full and maternal half-siblings and 0.0 for the paternal half-siblings. The liability-threshold model was used to account for the fact that we had included binary phenotypes and we relaxed assumptions of equal thresholds across the groups of siblings because the prevalence differences were non-negligible. All models adjusted for sex and cohort effects. We fitted equivalent twin models for the TCHAD replication sample.

The final models consisted of Cholesky decompositions, where we estimated the phenotypic correlations between schizophrenia and neighborhood deprivation in the sibling study and psychotic experiences and neighborhood deprivation in the twin study, respectively. We subsequently decomposed the phenotypic correlation into the contributions of genetic, shared and unique environmental influences.

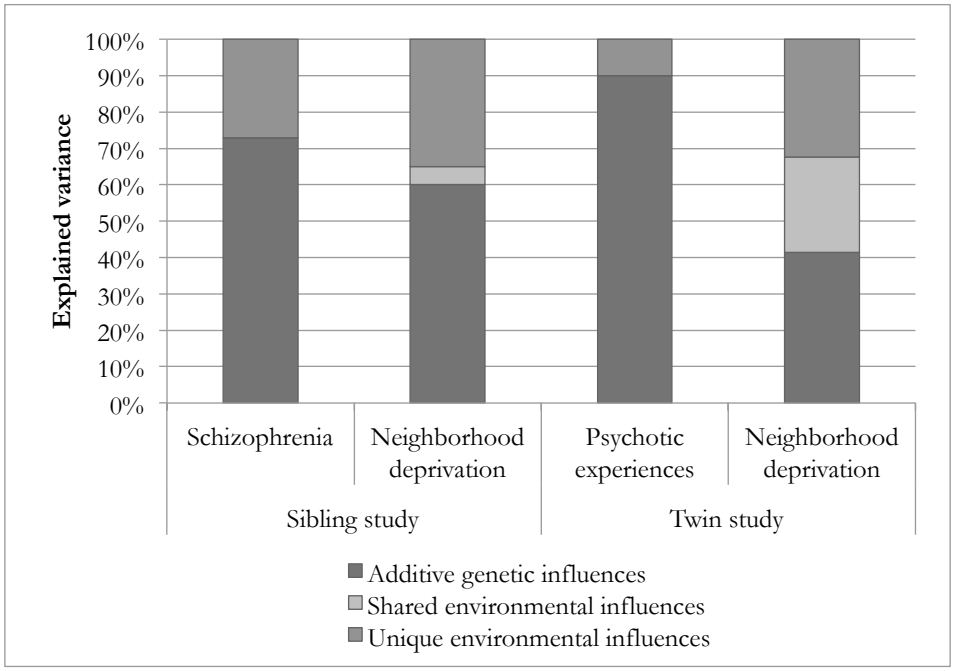
6.4.1 Results

6.4.1.1 Univariate models

The results of the univariate quantitative genetic models (Figure 6.7) for the sibling study demonstrated that schizophrenia had an estimated heritability of 73 percent and that the remaining variance was due to the unique environmental influences. Neighborhood deprivation was also considerably heritable with 60 percent of the variance being attributed to genetic influences. Shared environmental influences accounted for 5 percent of the variance while the remaining 35 percent was due to unique environmental influences.

For the twin study, we observed that the heritability of psychotic experiences was 90 percent. Although statistically significant, power issues led to a rather wide confidence interval for this estimate (95% CI: 0.59-0.98). Neighborhood deprivation was also found to be considerably heritable in the twin study with genetic influences accounting for 41 percent of the variance. Shared environmental influences were also strong, accounting 26 percent of the variance.

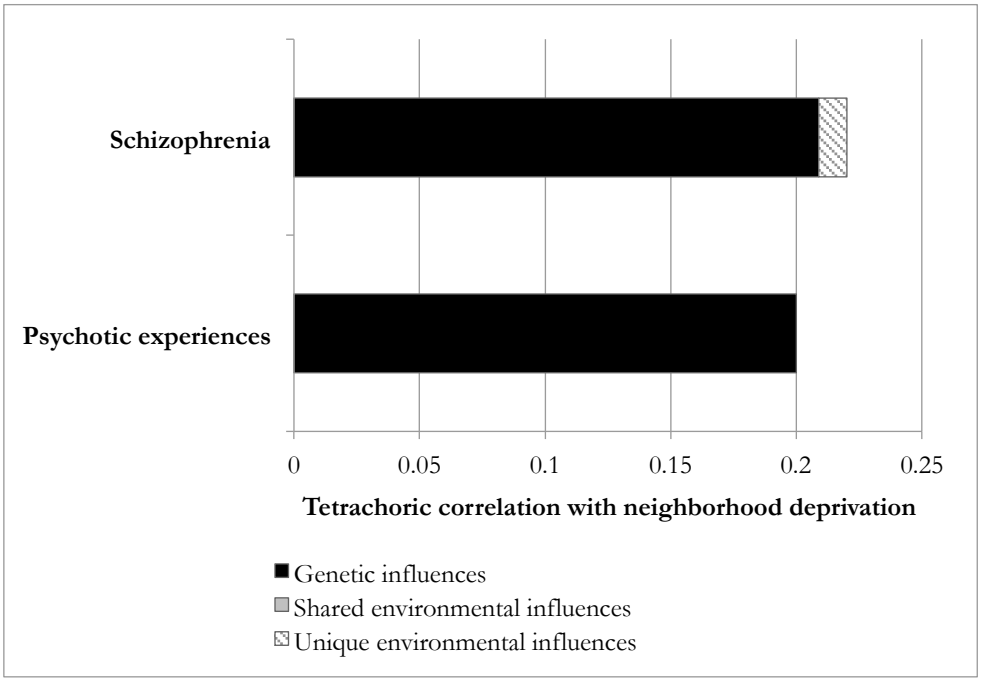
Figure 6.7 Univariate models for schizophrenia, psychotic experiences and neighborhood deprivation



6.4.1.2 Bivariate models

We found that the magnitude of the association between schizophrenia and neighborhood deprivation was relatively weak (r=0.22; Figure 6.8), an estimate that was fully replicated in the twin study. The decomposition of the correlation into genetic and environmental influences showed that the excess risks that schizophrenia patients faced to reside in deprived neighborhoods were fully explained by common genetic influences. The unique environmental influences were not significantly different from zero.

Figure 6.8 Tetrachoric correlations between schizophrenia, psychotic experiences and neighborhood deprivation, stratified by genetic and environmental influences



6.4.1.3 Sensitivity analyses

In supplementary sensitivity analyses, we tested whether broader definitions of neighborhood deprivation impacted our findings. Even with the broadest definition of the outcome, we still observed the common genetic influences accounted for 73 percent of the correlation between schizophrenia and neighborhood deprivation. Moreover, we tested whether a series of alternative specifications of shared environmental correlations for the half-siblings altered the findings but we failed to observe any meaningful deviations (e.g. the unique environmental influences were not significantly different from zero in any of the models).

7 DISCUSSION

7.1 GENERAL FINDINGS

7.1.1 The causal nature of the social causation hypothesis

Studies I–III examined whether exposure to socioeconomic and demographic conditions, measured on the community and family levels during childhood and adolescence, was causally related to the subsequent risk of being either convicted of violent criminality (Studies I and II), engaging in substance misuse (Studies I and II) or being diagnosed with schizophrenia (Study III). Consistent with previous findings based on standard epidemiological approaches that compare relative risks in unrelated individuals, we too observed that there were strong associations between the putative risk factors and the adverse outcomes. However, when we gradually accounted for unobserved familial confounders that were shared by differentially exposed cousins and siblings, we found that the risk increases were entirely attenuated within families. This suggest that the previously observed associations are not consistent with a causal inference as factors shared within families, genes and environments, are likely influencing both the parental self-selection into deprived and urban living conditions as well as the offspring's increased risks of violent criminality, substance misuse and psychiatric morbidity.

At the time when Studies I-III were conducted, we had no prior knowledge about the relative contributions of genes and environments to the liability of residing in Swedish deprived neighborhoods in adulthood. To our knowledge, this had not been tested in any other context either. We employed quantitative genetic sibling models in Study IV, which along with the complementary twin analyses presented herein (section 4.3.4) suggest that the heritability of deprived neighborhood residence in adulthood ranges between 50 and 60 percent. Shared environmental influences were also present but remained marginal in magnitude, accounting for a maximum of seven percent of the variance. These findings suggest that there are genetic, and to a lesser extent, shared environmental self-selection processes at work that drive individuals into deprived living conditions in adulthood. These findings further suggest that children are non-randomly exposed to deprived neighborhoods due to a combination of their parents' genetic and environmental influences.

7.1.2 The causal nature of the social drift hypothesis in schizophrenia

The primary aim of Study IV was to examine the etiology of the social drift hypothesis in schizophrenia. We expectedly found that schizophrenia patients experienced elevated risks of residing in deprived neighborhoods in their mid-30s. When we decomposed the correlation into genetic and environmental influences, we found that it was almost entirely accounted for by genetic influences. We were able to fully replicate these findings using a complementary nationally representative twin sample with measures on parent-reported auditory hallucinations during childhood and adolescence and residence in deprived neighborhoods in their early 20s. This implies that the association is not consistent with a causal inference because the excess risks that schizophrenia patients face in terms of residing deprived neighborhoods is explained the same genetic influences that increased their liabilities to develop disease.

7.2 METHODOLOGICAL CONSIDERATIONS

7.2.1 Misclassification bias

7.2.1.1 Criminal convictions

In studies I and II, we were confined to the use of official registry data on violent criminality, derived from the NCR, which encompasses all criminal conviction records in Sweden since the beginning of 1973. Despite its long-reaching coverage, it is well understood that a sizeable proportion of criminal acts do not come to the attention of the law enforcement. It has been argued that the examination of criminal propensity differences between groups of varying socioeconomic status is generally hindered by the fact that law enforcement officers tend to target deprived residential areas, which may explain why the residents in such areas have elevated rates of registered offences[389]. While there may be some merit to this argument, it has been repeatedly shown that the agreement between measures of official and newer instruments of self-reported criminality is very strong but that that official records tend to provide more false negative cases[390,391]. A large-scale nationally representative Swedish study nevertheless concluded that low socioeconomic status as measured by parental occupational status predicted measures of self-reported crimes and criminal convictions in a similar fashion[392]. This source of differential misclassification is not likely to have biased our conclusions as we found that siblings who were exposed to socioeconomically deprived

neighborhoods, with presumably concentrated police presence, did not differ from their unexposed siblings in regards to their risks of being convicted of criminal acts.

7.2.1.2 Schizophrenia

The use of single-episode schizophrenia diagnoses has been validated using the NPR[393]. It should, however, be noted that Swedish psychiatrists tend to follow the European tradition of cautiously diagnosing patients with the disorder, which implies that the mean age of the patient group, and in particular first-episode patients, tends to be higher than in other comparable countries[393-395]. The deinstitutionalization of psychiatric care following the 1995 Swedish Mental Health Care Reform meant that numerous schizophrenia patients were directed to receive their treatments in outpatient care facilities[396]. As a result of this change, the number of recorded schizophrenia patients in the NPR fell throughout the 1990s[397]. The outpatient care registry was established in 2001 but the non-participation of some clinics biased the estimates for psychiatric disorders up until 2006[398].

We ran a series of comprehensive sensitivity tests in Study III and IV, where we tested for different diagnostic definitions (number of episodes, in-care patient episodes only, broader definitions of non-affective psychosis etc.). The sensitivity tests were commensurate with our main findings. .

7.2.1.3 Childhood family income

Two potential sources of misclassification bias may marginally influence the measure of childhood family income. First, we lacked data on financial wealth during the measured period and had to rely solely on data measuring earnings and supplementary benefits provided by the government welfare transfer programs. Second, we aimed to get a measure of the entire material living standard that each children had theoretically access to. This is the reason for why we chose to calculate the average disposable income for both biological parents in case they had separated and lived with separate families. The data for children with separated parents may be biased for a number of reasons; there may be a large discrepancy in the earnings between the parents and the children may live with the parent who has the lowest earnings. It may also be the case that one of the parents cohabitates

with a new partner. The disposable family income will not include the earnings of the new partner unless they have a biological child with the parent[399]. Note that the analyses on childhood family income (Study II) matched corresponding analyses using neighborhood deprivation as exposure (Study I).

7.2.2 GLMMs

The popularity of GLMMs in social epidemiology has only recently been accompanied by a critical discussion of its assumptions among applied researchers[50,400]. A number of papers have specifically addressed differences between GLMMs and marginal and the interpretation of the estimates that they produce[358,401].

Study I constituted the first paper, to the best of my knowledge, which applied the between-within covariate parameterization in a cross-classified GLMM. In sensitivity tests, however, we re-ran the models using the same covariate parameterization but with cluster-robust standard errors to avoid making the strong distributional assumptions. In Study III, GLMMs were only used to derive general neighborhood effects. The covariate effects were all derived using different types of fixed-effects approaches.

In an invited commentary paper following the publication of Study I, Oakes[402] criticized the use of GLMMs for neighborhood studies due to the inherent identification problems. In regards to the paper specifically, he praised its ambitions to disentangle the specific effects of neighborhood deprivation from the familial influences but he argued that the research design was insufficient to achieve this goal. Both of these points will be addressed below.

Oakes is certainly right about the identification problems in GLMMs in terms of assessing neighborhood effects. The major limitation of the GLMM approach rests in the independence assumption between fixed and random effects, as well as between random effects. To simplify the point; GLMMs assume that factors that make neighborhoods different are unrelated to factors that make individuals different. To reiterate the points I made in section 5.2, the crude general neighborhood estimate is nearly always artificially inflated due to self-selection mechanisms (e.g., individuals suffering from illnesses will generally cluster in certain neighborhoods due to individual and familial risks that are non-randomly

distributed). This contributes to the paradoxical situation where the independence assumption implies that the clustering effects are causal and if one acknowledges such dependencies, the ICC estimates become largely meaningless to interpret. The second paradox of GLMMs is that the inclusions of observed individual and familial risks also violate the model assumptions, which makes it hard to accurately interpret the model parameters.

In his second point of criticism, Oakes raises a an interesting point that the differential exposures in the sibling-comparison models need to be sufficiently different in terms of the neighborhood deprivation scores so that the effects can be measured. The rationale for this argument being that if the siblings had lived in similarly deprived but different neighborhoods, then we would not expect there to be any meaningful differences between them in terms of their risks of the adverse outcomes. He writes that "[w]ithout some exogenous shock (e.g. injury, death, lottery, etc.), it is hard to imagine how this could come about."[402] (p. 1068).

The sibling correlation for the neighborhood derivation score was 0.46, which implies that over half (54%) of the variation in the neighborhood deprivation score varied within rather than between families. In addition, an excess of 80 percent of the siblings who were differentially exposed to neighborhoods had moved across at least one decile of the standardized neighborhood deprivation scale. The reason for the occurrence of these strong differences within families is most likely the exogenous shock that the major economic recession in the early 1990s implied.

7.2.3 The sibling-comparison design

The sibling-comparison design offers a powerful approach to account for selection factors shared by differentially exposed siblings[222,223,270]. However, the approach makes a number of strong assumptions that cannot always be met or even tested. Some of the assumptions (e.g., external validity, sibling contagion and carry-over effects) can be tested indirectly via complementary cousin-comparison analyses, provided that they generate consistent findings. This was the case in all of the studies that employed the cousin-comparison design (Study I-III); the within-extended family estimates were approximately half the size of the unrelated population estimates, despite the fact that cousins are assumed to only share 12.5 percent of their co-segregating genes. And while differentially exposed siblings

differed significantly from population controls in some cases, the differentially exposed cousins were only negligibly different from their population controls.

The role of measurement error in sibling-comparison models has been addressed recently[276]. It is well recognized that measurement error in an exposure leads to a bias of the estimate toward the null[403]. The within-family estimates derived from sibling-comparison models are based on the available information in a sub-sample (e.g., differentially exposed siblings), which limits the sample size and increases the measurement error. Simulation studies have shown that there is a theoretical bias that tends to emerge in the sibling-comparison in case the correlation between non-shared confounders is stronger than the shared familial confounders[276]. This is called a theoretical bias because it is not possible to estimate the needed parameters to assess potential magnitude of this source of bias.

If one finds these assumptions to be too strong, the alternative assumptions of non-experimental designs should be equally, if not more, discouraging. George Box is famously quoted for his observation that "all [statistical] models are wrong, but some are useful"[404]. Indeed, all statistical models make different assumptions and it is important to recognize them, and perhaps more important to test them. Different statistical models and research designs are developed to examine a specific aspect of a phenomenon. The triangulation of different approaches allows the researcher to draw inferences based on a more comprehensive evidence base. The family-based models provide great opportunities to test different causal hypotheses, especially when combined with nationwide registry data that can produce sufficient numbers of informative (e.g., differentially exposed) cases. A sibling-comparison model is not a "causal model" in the sense that one can test the causality of a given association between an exposure and an outcome; one can only determine whether an association is in line with a causal inference or not.

7.2.4 Quantitative genetic models

7.2.4.1 Equal environments assumption

The equal environments assumption (EAA) in the classical twin model assumes that both MZ and DZ twins have identical shared environmental influences, Critics have argued that the EAA is violated because MZ twins are more correlated in terms of their shared environments than DZ twins, which in turn causes an

upward bias of the heritability estimates[405]. Empirical findings suggests that the potential influence of this source of bias in minimal at best[406,407] and a recent simulation study concluded that the presence of EEA inflates heritability estimates up to a maximum of 5 percentage point[408].

It is possible that the EEA assumption is violated in quantitative genetic models that compares full and half-siblings (Study IV), in particular the assumption that paternal half-siblings do not share their childhood family environments[88,225]. However, the twin heritability estimates on neighborhood deprivation presented herein closely replicates the corresponding estimate in Study IV. In addition, we tested a number of alternative shared environmental correlations for the half-siblings and the results were consistent with the main findings of the paper.

7.2.4.2 Assortative mating

The assortative (non-random) mating assumption in the classical twin design assumes that the mating process in the population is random or, alternatively, that the parents of a given twin pair are not correlated in the measured phenotype of interest[228]. Strong phenotypic correlations between the parents violate the assumption that DZ twins share 50 percent of their co-segregating genes, which leads to lower heritability but higher shared environmental estimates[409]. Simulation studies have found that the bias resulting from assortative mating is generally quite modest[87,408].

7.2.4.3 Gene-environment interplay

The classical twin model assumes that the latent variables measuring the genetic and environmental influences are independent, which implies that gene-environment interplay, in the form of gene-environment correlation (rGE), gene-environment interaction (GxE) and epigenetic mechanisms[410] are assumed to be absent.

The classical twin design has been extended to the GxE model under strong assumptions (e.g., no genetic correlation between the phenotype and the moderator)[387,388]. A Swedish study using the TCHAD twin sample studied used the method to examine whether the genetic and environmental contributions of antisocial behaviors were moderated by neighborhood characteristics[411]. The authors concluded that environmental influences for the phenotype were more

pronounced in disadvantaged neighborhoods. The findings of Studies I-II, however, suggest that potential passive rGE may confound such moderated effects. There has been a growing interest in GxE models for antisocial and alcohol use disorder traits but the published studies seldom discuss confounding issues and the nature of the complex interplay between genetic and environmental influences[412,413].

The classic stress-diathesis hypothesis[414] has generated similar ideas in the etiological literature on schizophrenia, namely that putative environmental risks, such as urbanicity and social adversity, trigger the onset of the disorder, particularly in individuals with genetic liabilities[60,61,64,170,171,415]. Study III indicate that passive rGE may be an important consideration in the design of GxE studies in schizophrenia.

7.3 IMPLICATIONS

The studies included in this dissertation collectively demonstrate the importance of accurately accounting for unobserved familial confounders when examining the associations between putative environmental risk factors measured during childhood and adolescence and subsequent severe behavioral and psychiatric outcomes, specifically violent criminality, substance misuse and other psychiatric disorders. It was observed that deprived neighborhood residence in adulthood aggregated strongly in families, primarily due to genetic influences. Epidemiological studies that fail to account for such factors will therefore risk obtaining severely biased estimates that should be very cautiously interpreted.

It is important to stress that these findings do not imply that environmental factors are unimportant for the development of criminality, substance misuse and psychiatric morbidity. The purpose of the dissertation was to examine whether the effects of specific environmental exposures (e.g., neighborhood deprivation, family income, and population density) were causally associated with the adverse outcomes. The data failed to support such hypotheses.

Community-wide intervention efforts that specifically aim to decrease the rates of criminality, substance misuse and schizophrenia by diminishing socioeconomic differences between Swedish neighborhoods are, based on these findings, not likely to be successful. Such efforts may, however, be important for other outcome

measures that have not been considered here. Early prevention efforts should instead be directed towards identifying and supporting families with complex problems and dysfunctional family dynamics, whom have a high propensity to develop severe behavioral and psychiatric problems, regardless of their place of residence or socioeconomic status.

The generalizability of the findings presented in this dissertation is likely confined to the Scandinavian countries. It may be the case that neighborhood influences operating within countries characterized by more pronounced socioeconomic disparities do have an impact on the etiologies of the studied traits. However, it is important to recognize that the magnitude of the differences do not necessarily imply causation; selection factors must be adequately considered before such conclusions are drawn.

7.4 FUTURE RESEARCH DIRECTIONS

The sibling-comparison model adopted in this dissertation is unable to provide any information regarding the extent to which the familial confounders are due to genetic and/or environmental influences. This limitation occurs because it is impossible to disentangle the effects of genes and environments in pairs of differentially exposed siblings. Bivariate quantitative genetic models, such as the one conducted in Study IV, assume that both phenotypes are measured on the individual-level. In Studies I-III, the exposures were measured on the parental level (e.g., family income and neighborhood deprivation) and as such, both parents' genes and environmental influences contributed to the liabilities of those traits. It is currently possible to fit complex CoT/CoS models that can estimate the relative genetic and environmental contributions to the phenotypic correlation between a parental phenotype and an offspring phenotype[224]. The limitation of these models lies in the fact that only one of the parents can contribute to the phenotype[416]. Recent studies that have adopted such designs have studied the effects of maternal smoking during pregnancy on numerous adverse outcomes[289], maternal age at child birth on offspring ADHD[417] and paternal antisocial behaviors on offspring IQ[418]. The observed associations have generally been largely explained by common genetic influences, despite heterogeneous exposures and outcomes. Future research efforts should be directed toward the continued development of complex

intergenerational family-based research designs that can be applied to substantive social research questions.

Educational attainment remains to be the only socioeconomic status phenotype that has gained the widespread interest of both behavioral and molecular geneticists. The reasons for its popularity has to do with its historical connections to the intelligence phenotype that is well-researched in the field combined with the fact that it is relatively easy to measure cross-nationally (e.g., in contrast to income and occupational prestige). Earlier behavioral genetic twin studies on the trait suggested that the heritability varied roughly between 40 and 60 percent[419,420]. Our understanding of the underlying etiology has nevertheless been greatly advanced by the recent developments within molecular genetics. For instance, large-scale genome-wide association studies on educational attainment have identified nearly 70 common genetic variants that are associated with the trait and other related traits[421,422]. Another study has explored the etiological overlap between parental socioeconomic status and offspring IQ, as measured by common genetic variants in unrelated individuals using the genome-wide complex trait analysis (GCTA) approach[423]. The authors concluded that a majority of the associations were due to overlapping genetic influences.

In the light of these promising developments, it is particularly exciting to see that one of the largest twin studies in the world, the Child and Adolescent Twin Study in Sweden (CATSS) is in the process of genotyping their entire sample[195,424]. The major advances in the psychiatric genetics of schizophrenia have taught us that we need very large sample sizes to detect potentially informative genetic variants that may give us etiological clues as to the underlying mechanisms causing the phenotypes[425]. The updated CATSS sample will be able to contribute to the future collaborative efforts to find such etiological clues into the genetics of educational attainment. Importantly, it will also enable researchers to adopt molecular genetic tools, such as (multivariate) GCTA and polygenic risk scoring techniques to further explore the etiologies of other socioeconomic status measures, including neighborhood characteristics, and the intricate ways in which they relate to other behavioral and psychiatric phenotypes[426].

7.5 CONCLUSIONS

- **Study I** Residing in a deprived neighborhood during adolescence was associated with increased risks of violent criminality and substance misuse. This association was, however, entirely accounted for by unobserved familial confounders shared by differentially exposed siblings and was therefore not consistent with a causal inference.

- **Study II** Childhood family income was associated with increased risks of violent criminality and substance misuse. This association was, however, entirely accounted for by unobserved familial confounders shared by differentially exposed siblings and was therefore not consistent with a causal inference.

- **Study III** Residing in a deprived neighborhood or in an urban setting from birth up until adolescence was associated with increased risks of schizophrenia. These associations were, however, entirely accounted for by unobserved familial confounders shared by differentially exposed siblings and was therefore not consistent with a causal inference.

- **Study IV** Living in a deprived neighborhood in adulthood is a highly heritable trait with genetic influences explaining approximately 60 percent of its variation in the population. Individuals diagnosed with schizophrenia experienced elevated risks of residing in deprived neighborhoods. Their increased risks were attributed to common genetic influences that also influenced their risk of developing schizophrenia in the first place.

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